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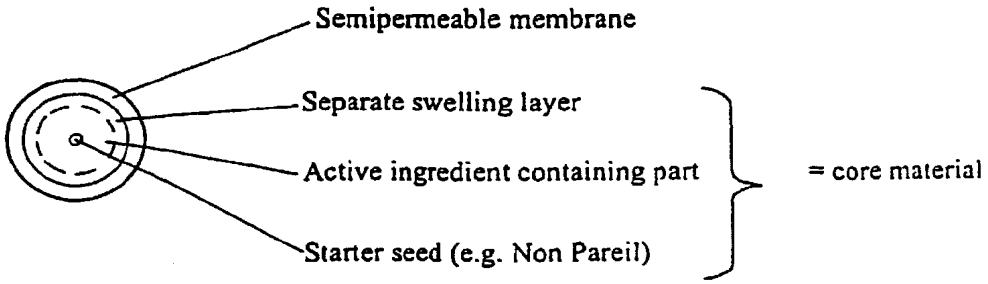

(57) Abstract: An oral dosage form comprising a core material coated with a semipermeable membrane wherein the core material comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, and the dosage form is not enteric coated.

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NEW FORMULATION

Field of the invention

The present invention relates to new oral pharmaceutical dosage forms comprising as active ingredient omeprazole, an alkaline salt of omeprazole, *S*-omeprazole or an alkaline salt of *S*-omeprazole. The dosage form comprises a core material of the active ingredient, one or more alkaline additives, and one or more swelling agents, wherein the core material is covered with a semipermeable membrane and without an enteric coating. Furthermore, the invention refers to the manufacture of such dosage forms and their use in medicine.

Background of the invention and prior art.

The acid labile H^+, K^+-ATPase inhibitor known under the generic name omeprazole is disclosed in EP-0005129. Certain salts of omeprazole are described in EP-124495, a magnesium salt of omeprazole is described in WO 95/01977, and the single enantiomers of omeprazole and certain salts thereof are described in WO 94/27988.

Omeprazole is useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrome. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease (GORD). Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis

as well as in the treatment of *Helicobacter* infections and diseases related to these where therapeutic control of gastric acid secretion is fundamental in the treatment.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light. With respect to the stability properties of omeprazole, it is established that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, US 4,786,505 describes such enteric coated formulations. These formulations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and further with an enteric coating layer. There are numerous published patent applications from different companies describing enteric coated formulations comprising omeprazole or other proton pump inhibitor compounds.

WO 96/01623 describes tableted dosage forms of omeprazole, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces.

There are different technologies and pharmaceutical formulations described in the prior art which provide a delayed release of an administered drug. Such formulations are for instance based on osmotic differences, slow-eroding/dissolving layers, diffusion through a membrane, time controlled explosion systems or any combinations thereof. In the following some of these principles are exemplified. For instance, US 4 871 549 describes a time controlled explosion system. Conte et al (Drug Development and Industrial

Pharmacy, 1989, vol. 15, pp. 2583 –96) describes a three-layer tablet giving a double pulsed system suitable for ibuprofen. US 5 567 441 describes a dosage form for diltiazem comprising a mixture of one fraction of slow release pellets and another fraction of delayed pulse release membrane coated pellets. WO97/02020 describes a dosage form of pantoprazole in combination with antibacterial substances wherein one part of the pantoprazole dose is in slow release form with a continuously release during time. US 5 178 867 describes a dosage form with an exit port or hole that connects the interior of the dosage form with the exterior.

Summary of the invention

The present invention provides - in contrast to earlier presented oral dosage forms for proton pump inhibitor compounds - a dosage form without an enteric coating layer.

The dosage form according to the present invention comprises a core material coated with a semipermeable membrane. The core material contains an active ingredient selected from omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof, one or more alkaline additives, and one or more swelling agents. The semipermeable membrane is able to disrupt or may change its permeability after a pre-determinated time. One or more swelling agents are placed in the core material to effectuate a disruption or an increased permeability of the semipermeable membrane after such a suitable time. Optionally pharmaceutically acceptable excipients such as an osmotic agent may also be included in the core material.

Surprisingly, the formulation according to the present invention is prepared without an enteric coating, which previously have been almost an axiom for dosage forms containing omeprazole or any other proton pump inhibitor compounds. The present invention also provides the possibility to avoid the separating layer needed under an enteric coating layer to separate omeprazole from the enteric coating polymer. Omeprazole should preferably not be in contact with the enteric coating due to discoloration and degradation of

omeprazole. Thus, the present invention provides a simplified process than previous manufacture processes requesting double coating layers on the core material. See for instance, EP 247 983.

According to a further aspect of the present invention, the dosage form may preferably be in the form of a multiple unit pellet system. The prepared core material, in the form of small pellets coated with a semipermeable membrane and without an enteric coating may be filled into a capsule or compressed into a multiple unit tablet.

The core material comprises an alkalizing agent, that is sufficiently alkaline and is present in a sufficiently high amount. The core material also comprises a swelling agent that upon contact with moisture starts to swell. When the coated pellets pass the stomach small amounts of gastric fluid will be absorbed through the semipermeable membrane. The alkalizing agent in the core material will neutralize the absorbed acidic fluid and protect the active ingredient against degradation. At the same time the swelling agent, will be exposed to the penetrating fluid or moisture, and it will start to expand. After a pre-determined time interval this expansion leads to disruption of the superimposed semipermeable membrane by the built-up pressure or to a swelling that will increase the permeability of the membrane. The time interval is to be determined so that the pellets have had time to pass the stomach at that very moment, and have reached the small intestines. The entire dose of the active ingredient will then start to be released into the small intestine where absorption can occur.

Detailed description of the drawings

Figures 1 – 4 illustrate principles for construction of dosage forms according to the present invention. The invention comprises a core material layered with a semipermeable membrane. The core material can be prepared according to at least four different principles as shown in the Figures. The drawings are not intended to illustrate the size or relative sizes of the dosage form or its different parts.

Detailed description of the invention

The present invention provides a core material in the form of pellets or small tablets coated with a semipermeable membrane. The composition of the core material protect the active ingredient against the gastric fluid, that permeates through the semi permeable coating during the pellet's passage through the stomach. Such pellet formulations are generally emptied from the stomach within 2-4 hours. When the pellets have left the stomach, the semipermeable membrane covering the individual pellets disrupts and/or starts to release the active ingredient in the small intestine.

The pellets coated with the semipermeable membrane may be filled into capsules prepared from gelatine or hydroxypropyl methylcellulose (HPMC), be filled into sachets or be mixed with tablet excipients and compressed to a fast disintegrating tablet or to an effervescent tablet.

Core material

The core material may be produced with starter seeds, for instance sugar spheres like Non-pareils™, by layering the active ingredient on the seeds by conventional technique or by the use of a centrifugal granulator/ roto granulator. Alternatively, the core material has a homogenous distribution of the active agent and excipients, and is prepared e.g. by extrusion and spheronization, or by compression. Other conventional techniques known in the art are also suitable in preparing the core material.

The core material is in the form of pellets, spheroids or small tablets. The size of the formulated core materials is approximately between 0.1 and 4 mm, and preferably the core material has a diameter of 0.2 to 2.5 mm.

The core material comprises the active ingredient, an alkalizing agent, a swelling agent and optionally binders, osmotic agents and other pharmaceutically acceptable excipients.

The active ingredient is selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof. Suitable alkaline salts are for instance the Mg^{2+}, Ca^{2+}, Na^{+}, K^{+} salts, preferably the Mg^{2+} salts in a highly crystalline form. A preferred magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffration is described in WO95/01977, hereby incorporated by references.

Before the seeds are layered, the active ingredient may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active ingredient in the final mixture.

Such further components can be binders, surfactants, fillers or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example cellulose derivatives such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, and others such as polyvinyl pyrrolidone, gelatine, sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulphate.

An alkalizing agent is incorporated in the core material together with the active ingredient and/or the swelling agent, preferably together with the active ingredient. The alkalizing agent is present in an amount of approximately 5 to 35 % w/w in the core material, preferably 10 to 35 % w/w, or most preferably 15 to 35 % by weight calculated on the weight of the core material excluding the weight of the optional starter seed.

The alkalizing agent is selected from compounds like disodium hydrogen phosphate, trisodium phosphate, arginine or talc etc, provided that they give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode. At least one alkalizing agent has to be incorporated in the core material, but also any combinations of alkalizing agents can be used.

The swelling agent is selected among pharmaceutically acceptable disintegrants, preferably among crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate or low-substituted hydroxypropyl cellulose (L-HPC), alone or in any combinations. The amount of swelling agent is pre-determined to effectuate the start of dissolution of the core material at a proper time. Preferably, the core material comprises approximately 20 to 60 % by weight of the swelling agent calculated on the weight of the core material excluding any optional starting seed. More preferably a concentration of 25 to 55 % by weight, or especially 30 to 50 % by weight of the swelling agent calculated in the same manner.

Alternatively, the swelling agent or a portion of the swelling agent may optionally be prepared and incorporated in a separate layer. Such a separate layer will cover the core material and also comprise binders and optionally an alkalizing agent and/or pharmacetically acceptable excipients.

Optionally, an osmotic agent is incorporated in the core material. Such an osmotic agent is watersoluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulphate, sodium chloride, lithium chloride, potassium chloride, potassium sulphate, sodium carbonate, lithium sulphate, calcium bicarbonate, sodium sulphate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

Alternatively, the active ingredient, optionally mixed with any of the components defined above, can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing different process equipments.

For extrusion/spheronization processes incorporation of a microcrystalline cellulose and a low-substituted hydroxypropylcellulose in the core material is preferred.

Semipermeable membrane.

The membrane comprises a water insoluble polymer and a modifying additive and optionally pharmaceutically acceptable excipients like fillers, colorants etc. The excipients should be insoluble or hardly soluble in acidic solutions, or present in such amounts that they do not influence the solubility properties of the membrane.

Preferably, water insoluble polymer may be selected among semipermeable water insoluble polymers like ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B (Eudragit RL, Eudragit RS) etc.

The modifying agent in the semipermeable membrane may be a talc or fumed silica (e.g. Aerosil or Cab-O-Sil.). Preferably an alkaline reacting modifying agent such as talc is used.

Preferred composition of the semipermeable membrane comprises an amount of modifying agent to water insoluble polymer on a weight to weight ratio of from 90:10 up to 50:50. Preferably the amount of modifying agent to water insoluble polymer on a weight to weight ratio is from 80:20 up to 60:40 in the membrane.

The core material will be layered with a sufficient amount of the semipermeable membrane composition to cover the core material. Preferably, the amount of semipermeable membrane applied is approximately 3-30% by weight of the weight of the core material. The amount of semipermeable membrane for a desired dosage form is adjusted to obtain a desired lagtime and an adequate dissolution.

Final dosage form

The prepared core material coated with the semipermeable membrane is filled into a capsule (gelatine or HPMC capsule), or optionally mixed with tablet excipients and compressed into a multiple unit tableted dosage form. In the expression "tablet excipients" is also effervescent tablet excipients included when referring to multiple unit tablets. Prepared tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and/or to further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The claimed dosage forms are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of severe conditions higher doses than average may be used.

Preferably, a dosage form comprising for instance 1 - 100 mg of omeprazole or S-omeprazole will be administered once a day. Suitable doses comprise preferably 10 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids.

Examples

The following examples describe the invention more in detail without restricting the scope of the invention.

Example 1

Core materials in the form of pellets made by extrusion and spheronization.

The following compositions were used to prepare core materials;

	Pellets A		Pellets B		Pellets C	
Compound	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets
Omeprazole	40.0		40.0		40.0	
Low-substituted Hydroxypropyl cellulose	82.0	20.6	-	-	84.0	21.0
Polyvinyl pyrrolidone crosslinked micronized	-	-	84.0	21.0	-	-
Microcrystalline cellulose PH 101	58.0		60.2		78.4	
Mannitol powder	136.0		115.0		136.5	
Sodium chloride (<0.20 mm)	60.0		20.0		40.3	
Trisodium phosphate*	20.0	4.8	-	-	-	-
Disodium hydrogen phosphate*	-	-	-	-	20.0	5.0
Arginine	-	-	80.0	20.0	-	-
Sodium lauryl sulphate	2.0		0.8		0.8	
Water purified	170	-	151	-	199	-
Total weight of dry subst.	418		400		400	

* In this example the amounts for all phosphates are indicated as free of crystal water.

The powders were mixed and then wetted with the granulating solution. When needed extra water was added afterwards, until total amount added water corresponded to the value given in the table above. The wet mass was subjected for extrusion through a screen having 1.0 mm in diameter apertures. The strings obtained were shaped to pellets in a

spheronizer operated at 350 rpm. The pellets were dried in a fluid bed apparatus with inlet air temperature set to 50 degrees Celsius.

Granulating liquid used for composition A was 2.72 g of the trisodium phosphate and all the sodium lauryl sulphate dissolved in 50 grams of the water.

Granulating liquid used for composition B was 10.0 g of the arginine and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Granulating liquid used for composition C was 8.06 g of the disodium hydrogen phosphate and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Remark: Only parts of composition B were possible to get through the extruder, however material for further experimentation was obtained.

Example 2

Core material in the form of pellets prepared by layering technique.

A drug containing suspension was made according to the composition below;

Compound	Amount
Omeprazole	219 g
HPMC, 6 cps	39.8 g
Disodiumhydrogen phosphate	42.9 g
Polysorbate 80	4.8 g
Purified water	919 g

First the polysorbate 80 was dissolved in the water. Then the phosphate was dissolved during stirring. Then the HPMC was dissolved whereafter the drug was suspended in the obtained solution. The suspension was sprayed onto 150 g of sugar spheres (Non-pareil) in

a fluidized bed. The weight of the obtained product was 355 g and the omeprazole content was 456 mg/g.

A suspension containing swellable substance was prepared according to the following composition;

		%
Cross-linked polyvinyl pyrrolidone micronized (Kollidon CL-M)	187.8 g	41*
Hydroxypropylcellulose L (HPC-L from Nisso)	46.9 g	
Talc	140.8 g	
EtOH (99.5%)	1500 g	

* % w/w of core material not including starter seed.

HPC-L was dissolved in ethanol during stirring, then the talc and swelling agent Kollidon CL-M was added. The suspension was sprayed onto 130 g of the drug-layered spheres as prepared above in a Wurster equipped fluidized bed until the omeprazole content of the obtained core material was 130 mg/g. The weight of the obtained product was 455 g.

Example 3

Membrane coated pellets.

The core material from Example 2 was coated in a fluid bed apparatus with an ethyl cellulose solution having talc suspended therein. The composition of the suspension used was:

Substance	Amount	% of dry membrane
Ethyl cellulose N-10	13.5 parts	30%
Ethanol (99.5%)	1455 parts	-
Talc	31.5 parts	70%
Total	1500 parts	100%

80 grams of core material from example 2 was coated with this suspension until the omeprazole content was 107 mg/g.

Example 4

Test of the prepared membrane coated pellets.

The prepared membrane coated core material was tested for gastric acid resistance and dissolution as described below.

Test for gastric acid resistance

The pellets were tested for gastric acid resistance by immersing them in 0.1 M HCl for 2 hrs and the determining the remaining drug fraction. The fluid phase (the HCl) had an addition of 0.1 g/liter of sodium lauryl sulphate as wetting agent. The remaining drug fraction was 96%.

Test for dissolution

Dissolution of active substance was tested accordingly, first pellets were immersed in the test-fluid described above for 2 hrs, then buffer components (phosphate salts) were added to change the pH to 6.8.

Samples of the dissolution medium were withdrawn and analyzed with HPLC at the given time intervals. Results;

Time , Hrs (after 2hrs of pre-exposure in acid medium)	% Dissolved
0.5	3
1	18
2	60
3	73

Claims

1. An oral dosage form comprising a core material coated with a semipermeable membrane wherein the core material comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, and the dosage form is not enteric coated

2. A dosage form according to claim 1 wherein the semipermeable membrane is able to disrupt.

3. A dosage form according to claim 1 wherein the active ingredient is omeprazole.

4. A dosage form according to claim 1 wherein the active ingredient is a magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffration.

5. A dosage form according to claim 1 wherein the active ingredient is magnesium salt of *S*-omeprazole.

6. A dosage form according to claim 1 wherein the core material comprises a sugar sphere layered with a suspension or solution of the active ingredient, one or more alkaline additives, one or more swelling agents and optionally pharmaceutically acceptable excipients.

7. A dosage form according to claim 1 wherein the dosage form comprises individual pellets of the core material coated with the semipermeable membrane.

8. A dosage form according to claim 1 wherein the core material comprises a further component in the form of an osmotic agent.

9. A dosage form according to claim 1 wherein the alkaline additive is an agent selected from the group of compounds that give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode.

10. A dosage form according to claim 9 wherein the alkaline additive is an agent selected from the group of disodium hydrogen phoshate, trisodium phosphate, arginine and talc.

11. A dosage form according to claim 1 wherein the alkaline additive is present in an amount of approximately 5 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

12. A dosage form according to claim 1 wherein the alkaline additive is present in an amount of 15 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

13. A dosage form according to claim 1 wherein the swelling agent is selected from the group of crossliked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC).

14. A dosage form according to claim 1 wherein the swelling agent is present in an amount of approximately 20 to 60 % by weight of the core material excluding the weight of an optional sugar sphere.

15. A dosage form according to claim 1 wherein the swelling agent is present in an amount of 30 to 50 % by weight of the core material excluding the weight of an optional sugar sphere.

16. A dosage form according to claim 1 wherein the semipermeable membrane comprises a water insoluble polymer and a modifying agent such as talc or fumed silica.

17. A dosage form according to claim 1 wherein the water insoluble polymer is selected from the group of ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B.

18. A dosage form according to claim 1 wherein the water insoluble polymer is present in an amount of approximately 3-30% by weight of the core material.

19. A dosage form according to claim 1 wherein the semipermeable membrane comprises a modifying agent and a water insoluble polymer in a ratio of between 90:10 and 50:50.

20. A process for the manufacture of a dosage form as defined in claim 1, wherein a core material is formed comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, the core material is coated with a semipermeable membrane and has no enteric coating.

21. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

22. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

23. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

24. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

Fig. 1

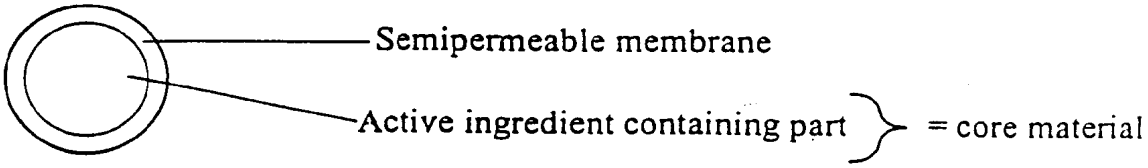


Fig. 2

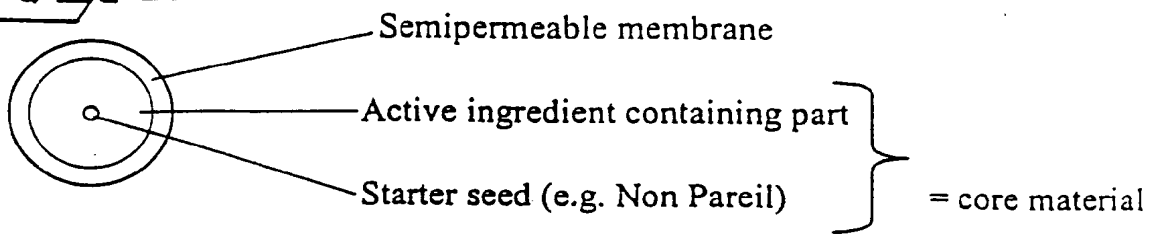


Fig. 3

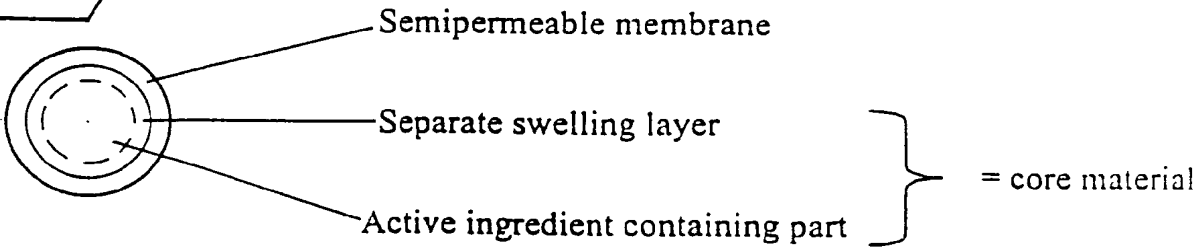
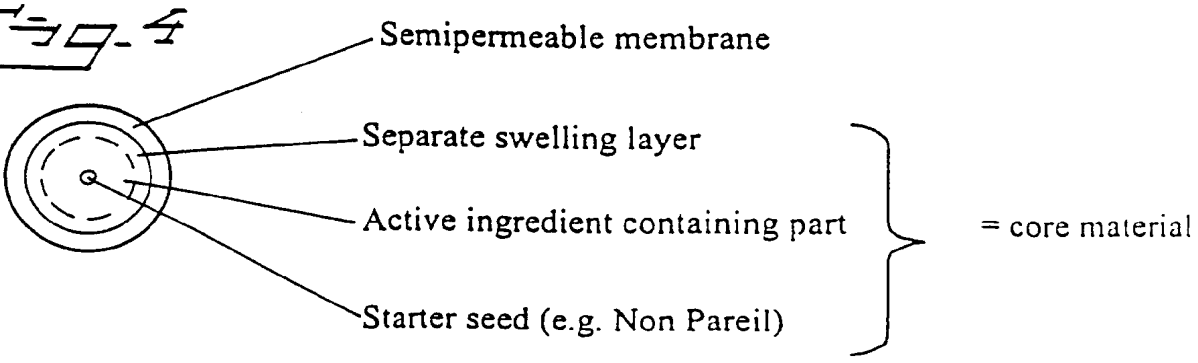


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01310

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/36, A61P 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0009092 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 24 February 2000 (24.02.00)	1-24
X	EP 0237200 A2 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 16 Sept 1987 (16.09.87), page 8, line 1 - page 9, line 8	1-24
Y	WO 9725979 A1 (PERIO PRIDUCTS LTD.), 24 July 1997 (24.07.97), page 10 - page 11	1-24
Y	WO 9819668 A1 (SHARMATED, INC.), 14 May 1998 (14.05.98), page 5, line 9 - page 6, line 25	1-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	18 -10- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hampus Rystedt/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01310

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9501783 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95)	1-24

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INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/SE00/01310

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23,24
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23 and 24 relate to methods for treatment of the human body, a search has been carried out. The search has been based on the alleged effects of the claimed composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/01310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/01310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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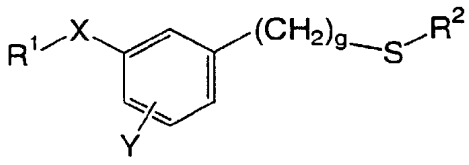
WO 01/34573 A1

(54) Title: COMPOUNDS



(I)

(57) Abstract: The invention relates to compounds of formula (I) which have anti-*Helicobacter pylori* activity.

COMPOUNDS

The present invention relates to compounds which have anti-*Helicobacter pylori* activity, i.e., compounds which can be administered to a mammalian patient therapeutically to treat *Helicobacter pylori* infection in the patient. The invention also relates to pharmaceutical formulations, use of a compound of the invention in the manufacture of a medicament, and processes for preparing the compounds.

Background to the Invention

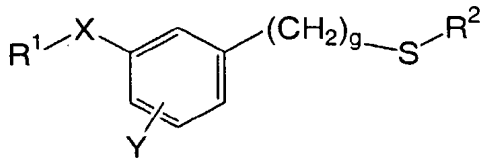
Helicobacter pylori is a gram negative bacterium which infects the human gastric mucosa. Infection with the bacterium causes inflammation of the gastric mucosa. Peptic ulceration of the duodenum or stomach can develop as well as adenocarcinomas or lymphomas of the stomach wall. Omeprazole (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole) is active against *Helicobacter pylori* (see Vogt, K and Hahn, H (1998), "Bactericidal Activity of Lansoprazole and Omeprazole against Helicobacter pylori in vitro", Drug Res. 48(1), No. 6, 694-697), and is labile towards rearrangement in acidic media. Omeprazole is a sulfoxide. This sulfoxide is labile towards rearrangement in acidic media and the rearrangement gives an intermediate, which is a potent proton pump inhibitor. Thus, the parent compound does not persist in the acidic environment of the stomach. Compounds related to omeprazole, where the sulphur atom is unoxidized are also active against *Helicobacter pylori*. However, these related compounds can undergo metabolic oxidation *in vivo* to give the corresponding sulfoxide, analagous to omeprazole, and have a propensitiy towards rearrangement in acidic media *in vivo* [J. Med. Chem. **1988**, *41*, 1777-1788]. Analogues which are potent against *Helicobacter pylori*, but not acid labile and thus stable in acidic media are desirable. Such analogues could be administered to a mammalian patient therapeutically to treat *Helicobacter pylori* infection.

In addition, it would be preferable for such analogues to be selective for *Helicobacter pylori*, since this is desirable to avoid the disruption of the normal gastrointestinal flora, and to reduce the incidence of bacterial resistance development.

Summary of the Invention

Accordingly, the present invention provides compounds of formula I or pharmaceutically acceptable salts or solvates thereof which are active against *Helicobacter pylori*, but lack the pyridine nitrogen of omeprazole and its analogues which is necessary for

rearrangement in acidic media. Thus, the compounds of the invention are more stable in acid media. Formula I is as follows:



I

wherein:

X is S; SO_2; NH; N(C_{1-6}alkyl); O or CH_2;

Y is C_{1-6}alkyl; O(C_{3-8}cycloalkyl); O(C_{1-6}alkyl); Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal , wherein Hal represents halogen; NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl, or NRR´ represents an optionally substituted C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; H; COOR″ or COR″, R″ representing H or C_{1-6}alkyl; or CH_2OH;

R^1 $-(CH_2)_a-R^3$; $-((CH_2)_bO)_c-R^3$; $-(CH_2)_d-R^{3'}$; $-(CH_2)_aC(=O)R^3$; $-(CH_2)_dC(=O)R^{3'}$; $-((CH_2)_e-O)_{c'}-(CH_2)_f-R^{3'}$; R^3 or $R^{3'}$.

R^2 is an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S;

R^3 is H; C_{1-6}alkyl; optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S;

$R^{3'}$ is -Z-M wherein Z represents O, S or NH and M represents H, an optionally substituted mono- or bi- cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, or an optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or -Z-M represents $-C(=O)NR^6R^7$, $-NR^6R^7$, $-OC(=O)NR^8R^9$, $-NC(=O)NR^8R^9$ or $-NC(=O)R^8$;

For R^4 and R^5, either:

(i) R^4 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; Z^2-(C_{1-8}alkyl)aryl, wherein Z^2 represents O or a bond, and the aryl is C6-10, optionally substituted and optionally fused to a C_{5-10} heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted C_{6-10}aryl; an

optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S; (C_{1-8}alkyl)-R, wherein R represents an optionally substituted mono- or bi-cyclic 5 to 10 membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted -C(=O)O(C_{1-8}alkyl); optionally substituted -C(=O)O-phenyl; optionally substituted -C(=O)(C_{1-8}alkyl); optionally substituted -C(=O)-phenyl; or -NC(=O)R^6 and

R^5 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10} and optionally substituted; optionally substituted C_{6-10}aryl; or an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or

(ii) the structure -NR^4R^5 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S and optionally fused to a C_{6-10} ring structure, -NR^4R^5 being optionally substituted;

For R^6 and R^7, either:

(i) R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10}; optionally substituted (C_{1-8}alkyl)R, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; or -C(=O)O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and R^7 is H; or

(ii) the structure -NR^6R^7 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S, -NR^6R^7 being optionally substituted;

a represents an integer 1, 2, 3, 4 or 5;

each b independently represents an integer 1, 2, 3, 4 or 5;

c represents an integer 1, 2, 3, 4 or 5;

c' represents an integer 1, 2, 3, 4 or 5;

d represents an integer 1, 2, 3, 4 or 5;

each e independently represents an integer 1, 2, 3, 4 or 5;

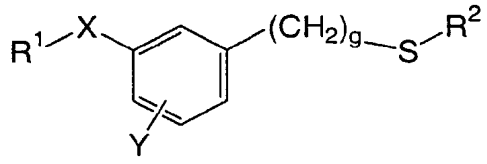
f represents an integer 1, 2, 3, 4 or 5; and

g represents zero or an integer 1, 2, 3, 4 or 5.

The invention also relates to pharmaceutical formulations, use of a compound of the invention in the manufacture of a medicament, processes for preparing the compounds and intermediates for use in such processes.

Detailed Description of the Invention

The present invention provides a compound of formula I or a pharmaceutically acceptable salt or solvate thereof



I

wherein:

X represents S; SO_2; NH; O or CH_2. Alternatively, X represents N(C_{1-6}alkyl), more preferably N-methyl or N(C_{2-4}alkyl).

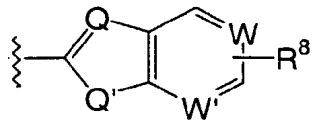
Y represents C_{1-6}alkyl (preferably C_{2-4}alkyl, and most preferably methyl); O(C_{3-8}cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C_{1-6}alkyl), preferably Omethyl or O(C_{2-4}alkyl); Hal, preferably Cl or F; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal , wherein Hal represents halogen (preferably F); NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl) , or NRR´ represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; H; COOR″ or COR″, R″ representing H or C_{1-6}alkyl (preferably methyl, ethyl); or CH_2OH. For optional substitution of the heterocyclic ring represented by NRR´, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl, -C(=O)O-*tert*-butyl or -C(=O)O(C_{3-6}alkyl); -C(=O)O-phenyl; -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -C(=O)OH; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br); NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

R^1 represents -$(CH_2)_a$-R^3; -$((CH_2)_bO)_c$-R^3; -$(CH_2)_d$-$R^{3'}$; -$((CH_2)_e$-$O)_c$'-$(CH_2)_f$-$R^{3'}$ (preferably where e=2 and f=2); R^3 or $R^{3'}$. Preferably, R^1 represents -$(CH_2)_a$-CH_3 or

-$((CH_2)_bO)_c$-CH_3. More preferably, R^1 is selected from –*iso*-Bu; -$(CH_2CH_2O)_3CH_3$; -(CH_2CH_2)-4-morpholinyl; -$(CH_2CH_2O)_5CH_3$; -(CH_2CH_2)-1-(2-methyl-5-nitro-imidazolyl); -(CH_2CH_2)-1-(1,2,4-triazolyl); and –(CH_2CH_2)-OC(=O)NH-Ph.

R^2 represents an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S. Preferred examples of the heterocycle are benzimidazolyl (preferably benzimidazol-2-yl), imidazolyl (preferably imidazol-2-yl), oxadiazolyl (preferably 1,3,4-oxadiazol-2-yl), pyrimidinyl (preferably pyrimidin-2-yl), tetrazolyl (preferably 1,2,3,4-tetrazol-5-yl), pyridinyl (preferably pyridin-2-yl or pyridin-4-yl), thiazolyl (preferably 1,3-thiazol-2-yl), pyridineimidazolyl (preferably pyridineimidazol-2-yl), benzoxazolyl (preferably 1,3-benzoxazol-2-yl), indolyl (preferably indol-2-yl). For optional substitution of the heterocycle, at least one (e.g., one, two or three) substituents may be provided independently selected from nitro; carboxylate; -COOH; =O; -S(=O)-(C_{1-8}alkyl), the alkyl preferably being methyl, ethyl or C_{3-6}alkyl; -S(=O)-(=O)-(C_{1-8}alkyl), the alkyl preferably being methyl, ethyl or C_{3-6}alkyl; halogen (preferably F or Cl); phenyl;
-O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; $OCHF_2$, OCH_2F, OCF_3; CHF_2, CH_2F, CF_3;
-C(=O)NRR′, wherein R and R′ are independently selected from H and C_{1-8}alkyl (preferably methyl, ethyl, propyl, isopropyl, or C_{2-6}alkyl), or the structure NRR′ represents an optionally substituted C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; and
- R″-NH(CO) R‴, wherein R″ represents C_{1-6}alkylene (preferably C_1 or C_2) and R‴ represents C_{1-6}alkyl (preferably C_1 or C_2).

In one preferred embodiment, R^2 represents



wherein:

Q is CH or N;

Q′ is NH, O or S;

W is CH or N;

W′ is CH or N; and

R^8 represents C_{1-6}alkyl (preferably C_{2-4}alkyl, and most preferably methyl); O(C_{3-8}cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C_{1-6}alkyl), preferably Omethyl or O(C_{2-4}alkyl); Hal, preferably Cl or F; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen (preferably F); NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl) , or NRR´ represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; H; $COOR^9$ or COR^9, R^9 representing H or C_{1-6}alkyl (preferably methyl, ethyl); or CH_2OH. For optional substitution of the heterocyclic ring represented by NRR´, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl, -C(=O)O-*tert*-butyl or -C(=O)O(C_{3-6}alkyl); -C(=O)O-phenyl; -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -C(=O)OH; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

R^3 represents H; C_{1-6}alkyl; optionally substituted C_{3-8}, preferably C_{3-6}, cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure (e.g., phenyl) optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S. Preferably, the cycloalkyl contains heteroatoms and is selected from morpholinyl (4-morpholinyl), piperazinyl (preferably 1-piperazinyl), tetrazolyl (preferably 1,2,3,4-tetrazol-2-yl), imidazolyl (e.g., 1-imidazolyl) and triazolyl (e.g., 1-(1,2,4-triazolyl)). Preferred examples of the C_{1-6}alkyl are preferably C_{2-4}alkyl, methyl and butyl (e.g., isobutyl). preferred examples of the heterocyclic ring structure are imidazopyridazine (more preferably 6-imidazo[1,2-*b*]pyridazine) and imidazolyl (more preferably 1-imidazolyl). For optional substitution of the cycloalkyl, aryl or heterocyclic ring, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl) and nitro.

$R^{3'}$ represents -Z-M wherein Z represents O, S or NH and M represents H, an optionally substituted mono- or bi- cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, or an optionally substituted C_{5-10}aromatic ring structure (e.g., phenyl) optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or -Z-M -C(=O)NR^6R^7, -NR^6R^7, -OC(=O)NR^8R^9, -NC(=O)NR^8R^9 or -NC(=O)R^8;

Preferably, the heterocyclic ring structure is selected from imidazopyridazine (more preferably 6-imidazo[1,2-*b*]pyridazine) and imidazolyl (more preferably 1-imidazolyl). For optional substitution of the aromatic or heterocyclic ring structure, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl) and nitro.

Most preferably, $R^{3'}$ is selected from -4-morpholinyl; -1-(2-methyl-5-nitro-imidazolyl); -1-(1,2,4-triazolyl); and -OC(=O)NH-Ph.

For R^4 and R^5, either:

(i) R^4 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; Z^2-(C_{1-8}alkyl)aryl, wherein Z^2 represents O or a bond, and the aryl is C_{6-10}, optionally substituted and optionally fused to a C_{5-10} heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted C_{6-10}aryl; an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S; (C_{1-8}alkyl)-R, wherein R represents an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted -C(=O)O(C_{1-8}alkyl); optionally substituted -C(=O)O-phenyl; optionally substituted -C(=O)(C_{1-8}alkyl); optionally substituted -C(=O)-phenyl; or -NHC(=O)R^6; and

R^5 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10} and optionally substituted; optionally substituted C_{6-10}aryl; or an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or

(ii) the structure -NR^4R^5 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S and optionally fused to a C_{6-10}ring structure, -NR^4R^5 being optionally substituted.

For R^4 in option (i), preferably the C_{1-8}alkyl or the C_{1-8}alkyl in Z^2-(C_{1-8}alkyl)aryl or the C_{1-8}alkyl in (C_{1-8}alkyl)-R or the C_{1-8}alkyl in -C(=O)O(C_{1-8}alkyl) or the C_{1-8}alkyl in -C(=O)(C_{1-8}alkyl) is selected from C_{2-6}alkyl, methyl, ethyl, propyl (e.g., isopropyl), butyl (e.g., isobutyl or *tert*-butyl) and pentyl. Preferably, where C_{6-10}aryl is mentioned, the aryl is phenyl. Preferably, Z^2-(C_{1-8}alkyl)aryl represents Z^2-(C_{1-8}alkyl)benzodioxol. Preferably, for R^4, where a heterocyclic ring structure is mentioned, this is selected from furyl (e.g., 2-furyl), tetrahydrofuranyl (e.g., tetrahydro-2-furanyl), thienyl (e.g., 2-thienyl), morpholinyl (e.g., 4-morpholinyl), isoxazolyl (e.g., 4-isoxazolyl or 5-isoxazolyl), dioxoimidazolidinyl (e.g., 2,5-dioxoimidazolidinyl), pyrazinyl, dioxotetrahydropurinyl (e.g., 2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl), benzofuranyl (e.g., 2-benzofuranyl), pyridyl (e.g., 2-pyridyl or 3-pyridyl), quinolyl (e.g., 4-quinolyl), pyrrolidinyl (e.g., 2-pyrrolidinyl), piperazinyl (e.g., 1-piperazinyl), imidazopyridazinyl (e.g., imidazo[1,2-*b*]pyridazinyl) and tetrazolyl (e.g., tetrazol-2-yl, 1,2,3,4-tetrazol-2-yl). Preferably, for Z^2-(C_{1-8}alkyl)aryl, the aryl is optionally fused to a heterocyclic ring structure selected from furan, tetrahydrofuran, thiophene, morpholine, isoxazole, dioxoimidazolidine (e.g., 2,5-dioxoimidazolidine), pyrazine, dioxotetrahydropurine (e.g., 2,6-dioxo-1,2,3,6-tetrahydro-purine), benzofuran, pyridine, quinoline, pyrrolidine, piperazine, imidazopyridazine (e.g., imidazo[1,2-*b*]pyridazine) and tetrazole (e.g., 1,2,3,4-tetrazole). Preferably, the C_{3-8}cycloalkyl is selected from cyclopropyl C_{4-6}cycloalkyl and cyclopentyl. For optional substitution of the cycloalkyl, aryl, heterocycle or heterocyclic ring structure, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl or -C(=O)O(C_{3-6}alkyl); -C(=O)O-phenyl; -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

For option (ii), the C_{3-8}heterocyclic ring is preferably selected from piperidinyl (e.g., 1-piperidinyl), piperazinyl (e.g., 1-piperazinyl), morpholinyl (e.g., 4-morpholinyl) and tetrazolyl (e.g., 1,2,3,4-tetrazol-2-yl). Preferably, the C_{6-10} ring structure is selected from cyclohexyl and a benzo ring. For optional substitution of -NR^4R^5, at least one(e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-

ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl, -C(=O)O-*tert*-butyl or -C(=O)O(C_{3-6}alkyl); -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -C(=O)OH; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

For R^6 and R^7, either:

(i) R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10}; optionally substituted (C_{1-8}alkyl)R, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; or -C(=O)-O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and R^7 is H; or

(ii) the structure -NR^6R^7 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S and optionally fused to a C_{6-10}ring structure, -NR^6R^7 being optionally substituted.

For R^6 in option (ii), preferably C_{1-12}alkyl is selected from C_{1-8}alkyl, C_{2-6}alkyl, methyl, propyl (e.g., isopropyl), butyl (e.g., isobutyl or *tert*-butyl), pentyl and adamantyl (e.g., 1-adamantyl). For C_{1-8}alkyl in (C_{1-8}alkyl)aryl or (C_{1-8}alkyl)R, the alkyl is selected from C_{2-6}alkyl, methyl, propyl (e.g., isopropyl), butyl (e.g., isobutyl or *tert*-butyl) and pentyl. Preferably, where C_{6-10}aryl is mentioned, the aryl is phenyl. Preferably, Z^2-(C_{1-8}alkyl)aryl represents Z^2-(C_{1-8}alkyl)benzodioxol. Preferably, where a 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle is mentioned, this is selected from benzofuryl (e.g., benzofur-2-yl), furyl (e.g., 2-furyl), tetrahydrofuranyl (e.g., tetrahydro-2-furanyl), thienyl (e.g., 2-thienyl), morpholinyl (e.g., 4-morpholinyl), isoxazolyl (e.g., 4-isoxazolyl or 5-isoxazolyl), dioxoimidazolidinyl (e.g., 2,5-dioxoimidazolidinyl), pyrazinyl, dioxotetrahydropurinyl (e.g., 2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl), benzofuranyl (e.g., 2-benzofuranyl), pyridyl (e.g., 2-pyridyl or 3-pyridyl), quinolyl (e.g., 4-quinolyl), pyrrolidinyl (e.g., 2-pyrrolidinyl), piperazinyl (e.g., 1-piperazinyl), imidazopyridazinyl (e.g., imidazo[1,2-*b*]pyridazinyl) and tetrazolyl (e.g., tetrazol-2-yl, 1,2,3,4-tetrazol-2-yl). Preferably, the C_{3-8}cycloalkyl is selected from cyclopropyl C_{4-6}cycloalkyl and cyclopentyl. For optional substitution of the cycloalkyl, alkylaryl, aryl or

heterocycle, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl, -C(=O)O-*tert*-butyl or -C(=O)O(C_{3-6}alkyl); -C(=O)O-phenyl; -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -C(=O)OH; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

For option (ii), the C_{3-8}heterocyclic ring is preferably selected from piperidinyl (e.g., 1-piperidinyl), piperazinyl (e.g., 1-piperazinyl), morpholinyl (e.g., 4-morpholinyl) and tetrazolyl (e.g., 1,2,3,4-tetrazol-2-yl). Preferably, the C_{6-10}ring structure is selected from cyclohexyl and a benzo ring. For optional substitution of -NR^6R^7, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl or -C(=O)O(C_{3-6}alkyl); -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

In formula I, a represents 1, 2, 3, 4 or 5 (preferably 1 or 2); each b independently represents 1, 2, 3, 4 or 5 (preferably 1 or 2); c represents 1, 2, 3, 4 or 5 (preferably 1 or 2); c' represents 1, 2, 3, 4 or 5 (preferably 1 or 2); d represents 1, 2, 3, 4 or 5 (preferably 1 or 2); each e independently represents 1, 2, 3, 4 or 5 (preferably 1 or 2); f represents 1, 2, 3, 4 or 5 (preferably 1 or 2); and g represents zero or represents 1, 2, 3, 4 or 5 (preferably 1 or 2).

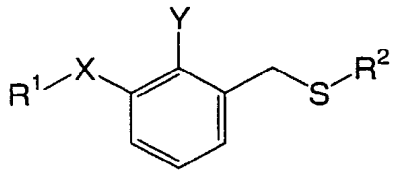
In the present specification, unless otherwise indicated, an alkyl substituent may be linear or branched.

Where optional substitution of aryl is mentioned, the substituent can be selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, and most preferably methyl); O(C_{3-8}cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C_{1-6}alkyl), preferably Omethyl or O(C_{2-4}alkyl); Hal, preferably Cl or F; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen (preferably F); NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl) , or NRR´ represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally

containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; H; COOR″ or COR″, R″ representing H or C_{1-6}alkyl (preferably methyl, ethyl); or CH_2OH. For optional substitution of the heterocyclic ring represented by NRR´, at least one (e.g., one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C_{1-8}alkyl), preferably -O-methyl, -O-ethyl or -O(C_{3-6}alkyl); -C(=O)O(C_{1-8}alkyl), preferably -C(=O)O-methyl, -C(=O)O-ethyl, -C(=O)O-*tert*-butyl or -C(=O)O(C_{3-6}alkyl); -C(=O)O-phenyl; -O-phenyl; -C(=O) (C_{1-8}alkyl), preferably -C(=O)-methyl, -C(=O)-ethyl or -C(=O)(C_{3-6}alkyl) ; -C(=O)OH; -S(C_{1-8}alkyl), preferably -S-methyl, -S-ethyl or -S(C_{3-6}alkyl); OH; halogen (e.g., F, Cl or Br), NRR' where R and R' are independently H or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

In one embodiment, a is 1, 2 or 3; b is 2; c' is 1, 2, 3, 4 or 5; d is 1, 2 or 3; e is 2; f is 1, 2 or 3; and g is 1 or 2.

Another embodiment has the general structure Ib



Ib

wherein:

X is S, S(=O), $S(=O)_2$ or O.

Y is C_{1-6}alkyl, O(C_{1-6}alkyl), Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal.

R^1 is $-(CH_2)_a-R^3$, $-((CH_2)_2O)_c-R^3$, $-(CH_2)_d-R^{3'}$, $-(CH_2)_aC(=O)R^3$, $-(CH_2)_dC(=O)R^{3'}$, $-((CH_2)_2O)_{c'}-(CH_2)_f-R^{3'}$.

R^3 is C_{1-6}alkyl; optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle.

$R^{3'}$ is -Z-M wherein Z represents O, S or NH and M represents H, an optionally substituted mono- or bi- cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure

containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or an optionally substituted C_{5-10} aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or -Z-M represents $-C(=O)NR^6R^7$, $-NR^6R^7$, $-OC(=O)NR^8R^9$, $-NC(=O)NR^8R^9$ or $-NC(=O)R^8$.

For R^6 and R^7, either:

(i) R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10}; optionally substituted (C_{1-8}alkyl)R, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or -C(=O)-O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and

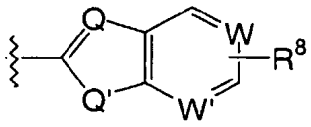
R^7 is H; or

(ii) the structure $-NR^6R^7$ represents a C_{3-8} heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; $-NR^6R^7$ being optionally substituted.

In one variation of the above embodiments, X is S or O; R^1 is $-(CH_2)_2R^3$, $-(CH_2)_2R^{3'}$, $-CH_2C(=O)R^3$ or $-CH_2C(=O)R^{3'}$; and R^3 is optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S.

In another variation of the above embodiments, R^1 is selected from *-iso*-Bu, $-(CH_2CH_2O)_3CH_3$, $-(CH_2CH_2)$-4-morpholinyl, $-(CH_2CH_2O)_5CH_3$, $-(CH_2CH_2)$-1-(2-methyl-5-nitro-imidazolyl), $-(CH_2CH_2)$-1-(1,2,4-triazolyl), and $-(CH_2CH_2)$-OC(=O)NH-Ph.

In still another variation of the above embodiments, R^2 represents



wherein:

Q is CH or N;

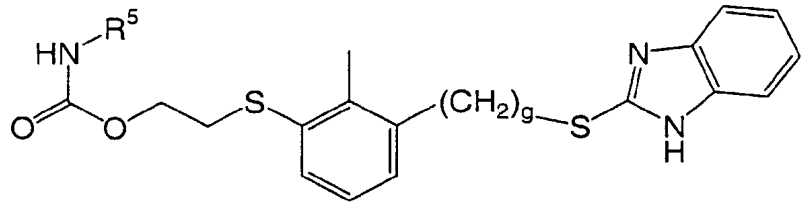
Q´ is NH, O or S;

W is CH or N;

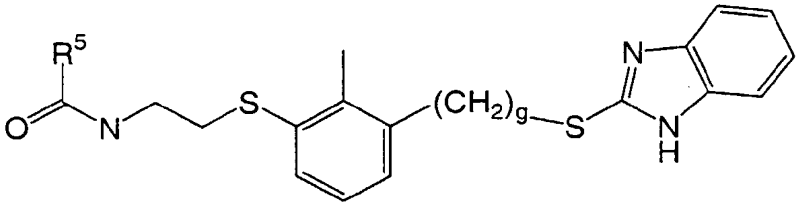
W´ is CH or N; and

R^8 is C_{1-6}alkyl; O(C_{3-8}cycloalkyl); O(C_{1-6}alkyl); Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen; NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl, or NRR´ represents an optionally substituted C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S; H; $COOR^9$ or COR^9, R^9 representing H or C_{1-6}alkyl; or CH_2OH.

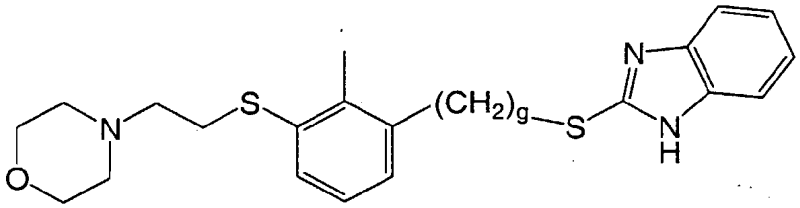
Preferred compounds are selected from compounds II, III, IV and V



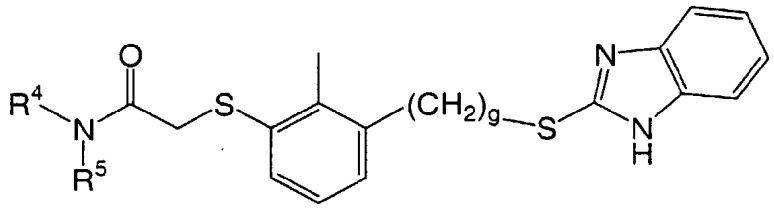
II



III



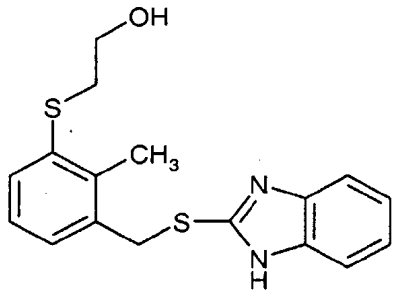
IV



V

Specific examples of compounds according to the invention are given below. Mass spectral molecular ion data are reported in units of m/z (mass/charge) in Daltons.

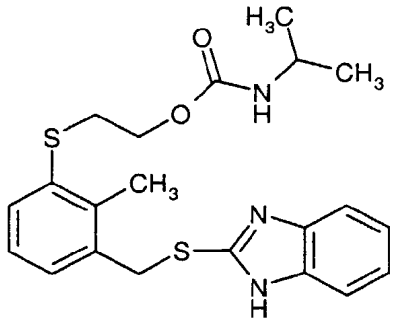
Compound 1



Mass spec' molecular ion: M+H= 331

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol

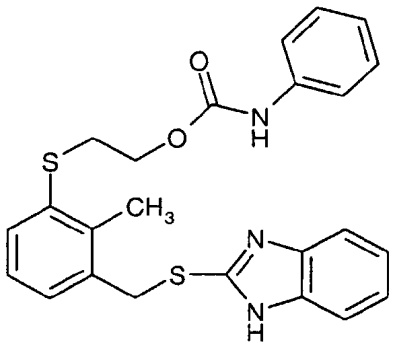
Compound 2



Mass spec' molecular ion: M+H=417

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl isopropylcarbamate

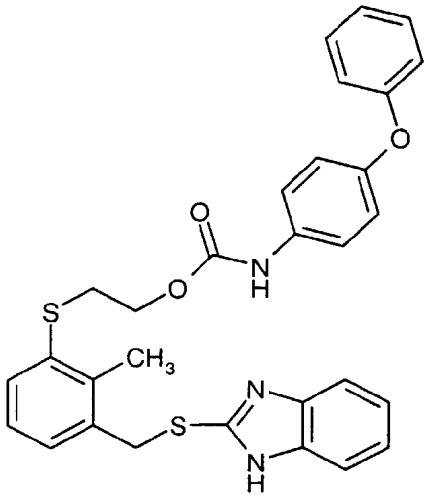
Compound 3



Mass spec' molecular ion: M+H= 450

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate

Compound 4

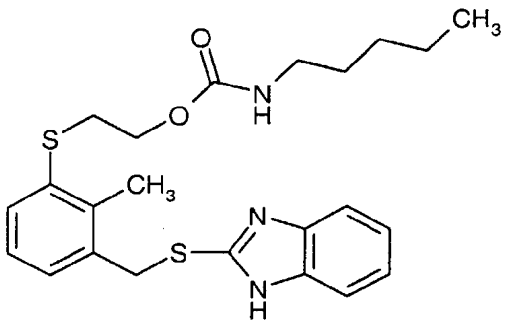


NMR:

^{1}H NMR (dmso-*d*6) ppm 2.42 (s, 3H), 3.26 (t, *J*=6.7 Hz, 2H), 4.22 (t, *J*=6.7 Hz, 2H), 4.62 (s, 2H), 6.95-7.68 (m, 16H), 9.57 (s, 1H, N*H*), 12.61 (s, 1H, N*H*).

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-phenoxyphenylcarbamate

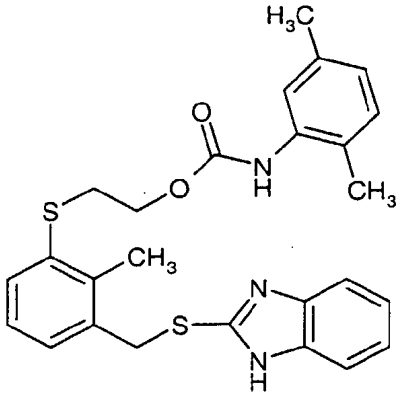
Compound 5



Mass spec' molecular ion: M+H= 445

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl pentylcarbamate

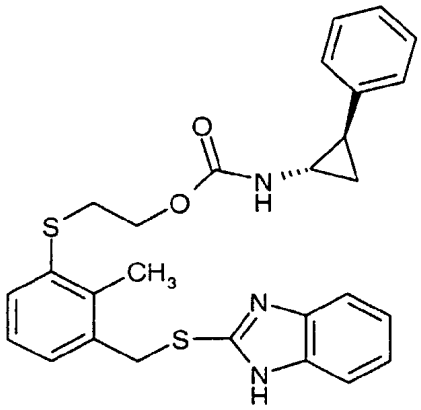
Compound 6



Mass spec' molecular ion: M+H= 479

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,5-dimethylphenylcarbamate

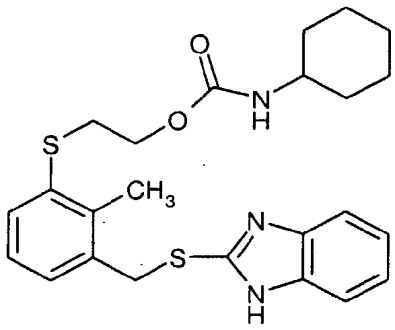
Compound 7



Mass spec' molecular ion: M+H= 490

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl (1*S*,2*R*)-2-phenylcyclopropylcarbamate

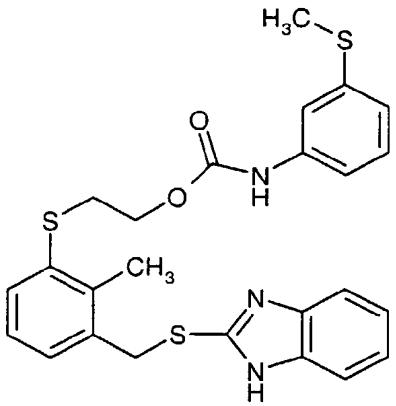
Compound 8



Mass spec' molecular ion: M+H= 456

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl cyclohexylcarbamate

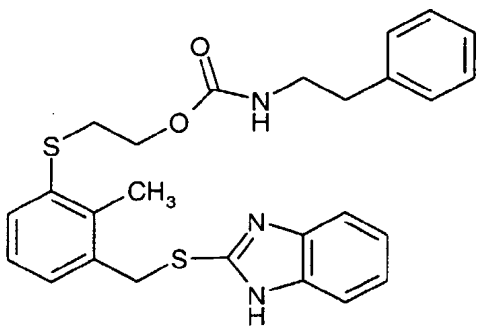
Compound 9



Mass spec' molecular ion: M+H= 496

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-(methylsulfanyl)phenylcarbamate

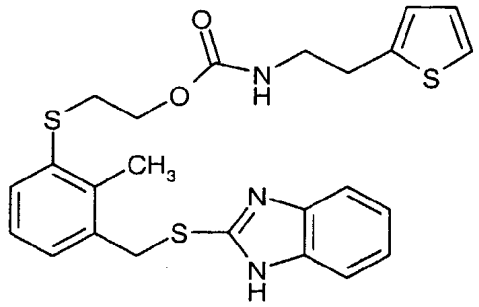
Compound 10



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenethylcarbamate

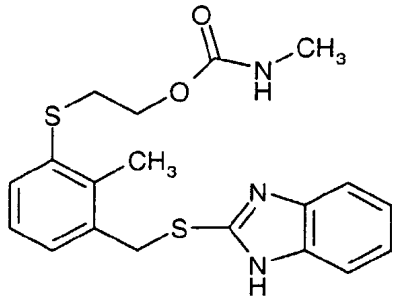
Compound 11



Mass spec' molecular ion: M+H= 484

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-(2-thienyl)ethylcarbamate

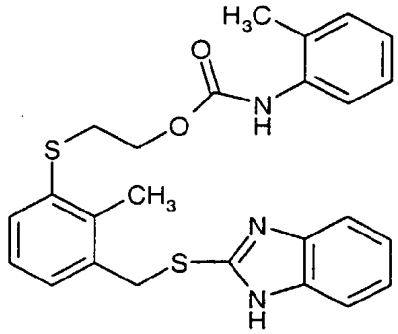
Compound 12



Mass spec' molecular ion: M+H= 388

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl methylcarbamate

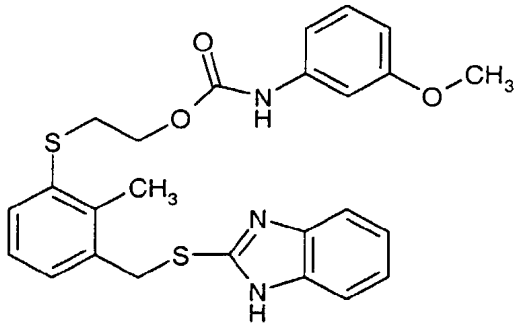
Compound 13



Mass spec' molecular ion: M+H= 464

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-methylphenylcarbamate

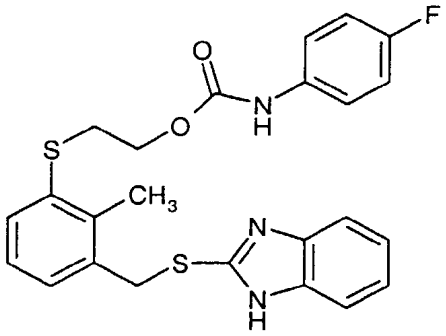
Compound 14



Mass spec' molecular ion: M+H= 480

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-methoxyphenylcarbamate

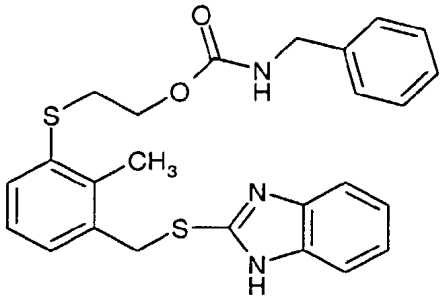
Compound 15



Mass spec' molecular ion: M+H= 468

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-fluorophenylcarbamate

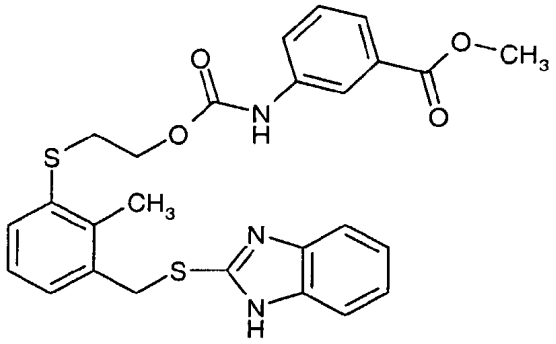
Compound 16



Mass spec' molecular ion: M+H= 464

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl benzylcarbamate

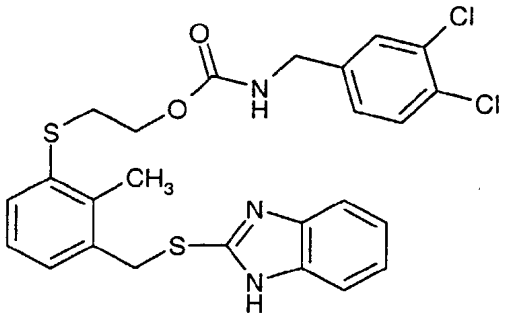
Compound 17



Mass spec' molecular ion: M+H= 508

methyl 3-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-ethoxy]carbonyl}amino)benzoate

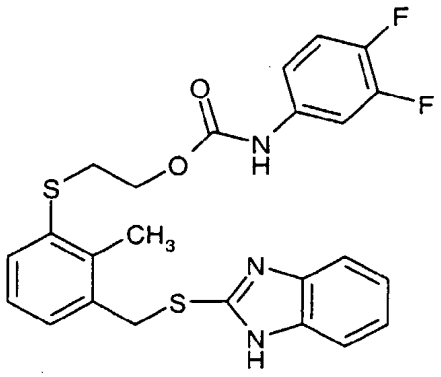
Compound 18



Mass spec' molecular ion: M+H= 532

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-dichlorobenzylcarbamate

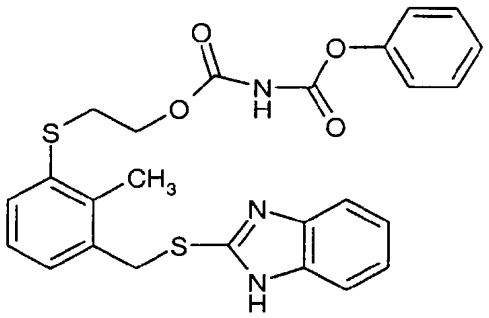
Compound 19



Mass spec' molecular ion: M+H= 486

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-difluorophenylcarbamate

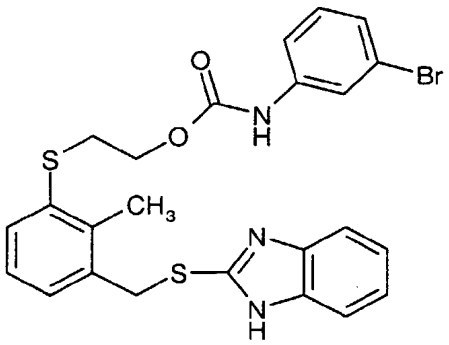
Compound 20



Mass spec' molecular ion: M+H= 494

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenyl dicarbonimidoate

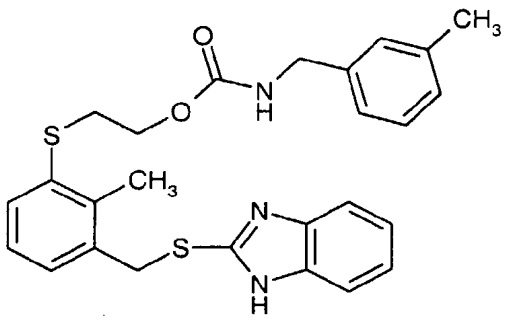
Compound 21



Mass spec' molecular ion: M+H= 529

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-bromophenylcarbamate

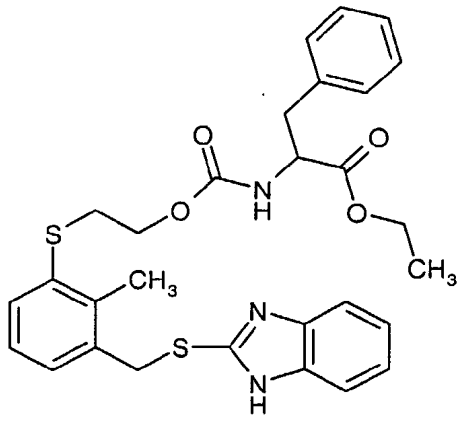
Compound 22



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-methylbenzylcarbamate

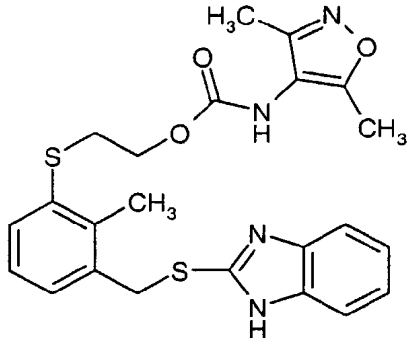
Compound 23



Mass spec' molecular ion: M+H= 550

ethyl 2-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]-carbonyl}amino)-3-phenylpropanoate

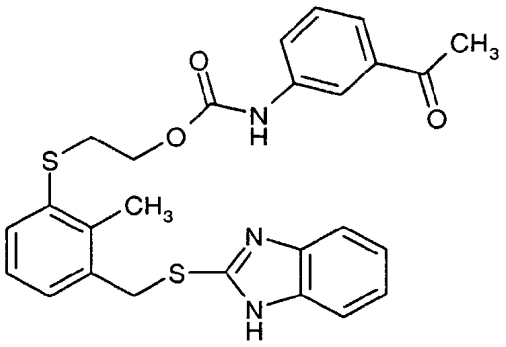
Compound 24



Mass spec' molecular ion: M+H= 469

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,5-dimethyl-4-isoxazolylcarbamate

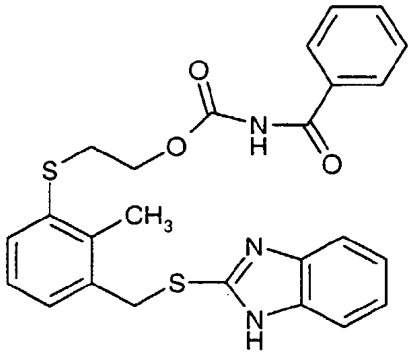
Compound 25



Mass spec' molecular ion: M+H= 492

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-acetylphenylcarbamate

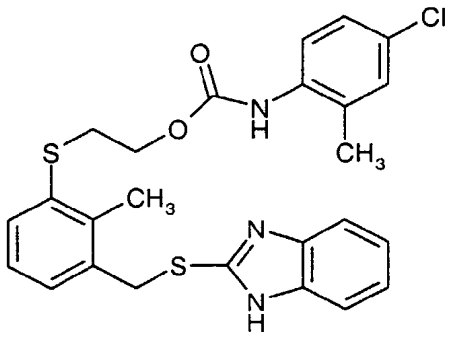
Compound 26



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl benzoylcarbamate

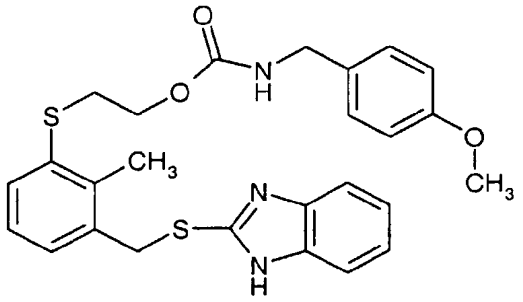
Compound 27



Mass spec' molecular ion: M+H= 499

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-chloro-2-methylphenylcarbamate

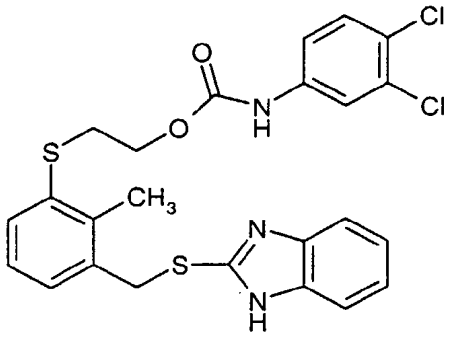
Compound 28



Mass spec' molecular ion: M+H= 494

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-methoxybenzylcarbamate

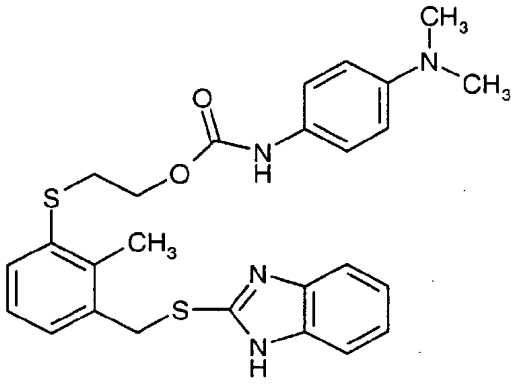
Compound 29



Mass spec' molecular ion: M+H= 518

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-dichlorophenylcarbamate

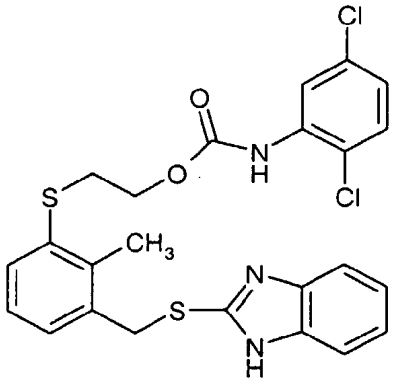
Compound 30



Mass spec' molecular ion: M+H= 493

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-(dimethylamino)phenylcarbamate

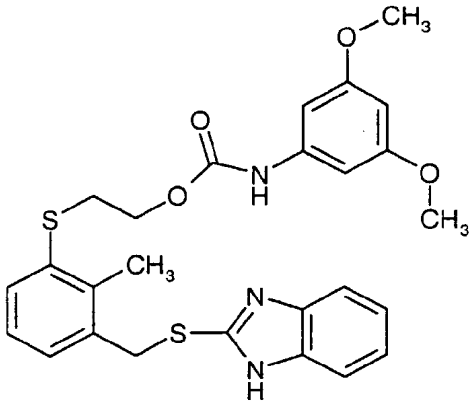
Compound 31



Mass spec' molecular ion: M+H= 518

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,5-dichlorophenylcarbamate

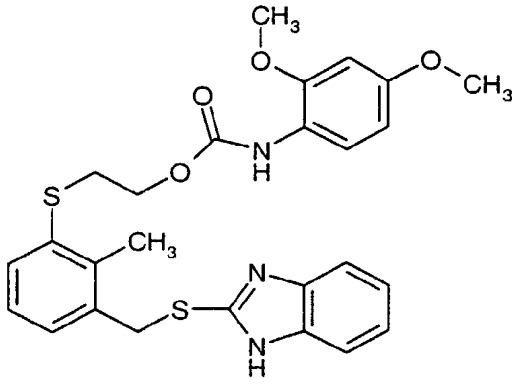
Compound 32



Mass spec' molecular ion: M+H= 510

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,5-dimethoxyphenylcarbamate

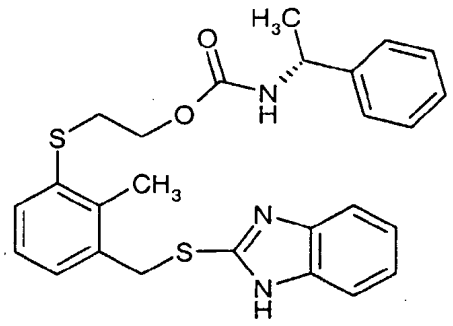
Compound 33



Mass spec' molecular ion: M+H= 510

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,4-dimethoxyphenylcarbamate

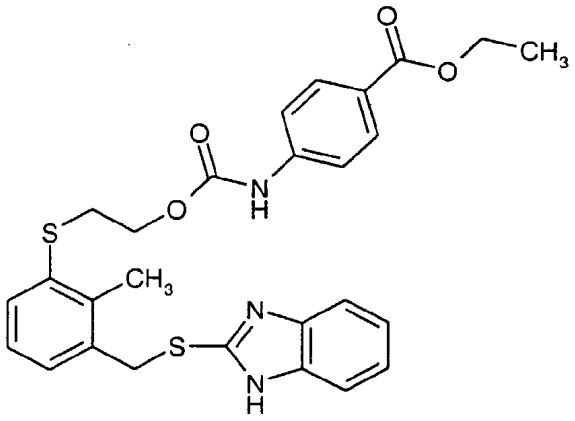
Compound 34



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl (1*R*)-1-phenylethylcarbamate

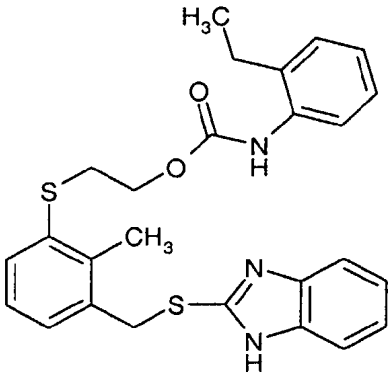
Compound 35



Mass spec' molecular ion: M+H= 522

ethyl 4-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}amino)benzoate

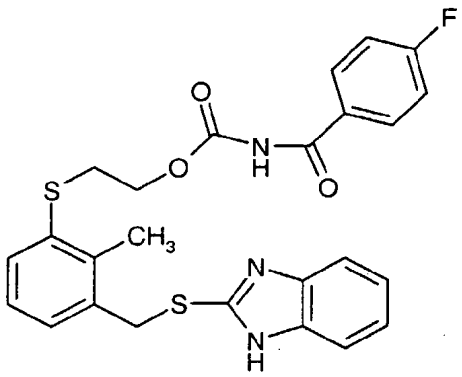
Compound 36



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-ethylphenylcarbamate

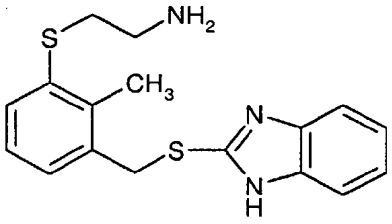
Compound 37



Mass spec' molecular ion: M+H= 496

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-fluorobenzoylcarbamate

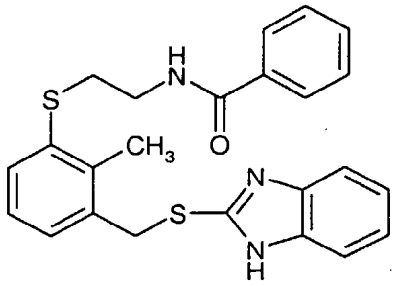
Compound 38



Mass spec' molecular ion: M+H= 330

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine

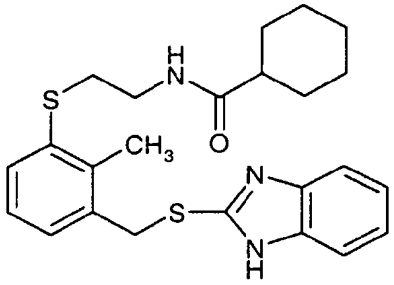
Compound 39



Mass spec' molecular ion: M+H= 434

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]benzamide

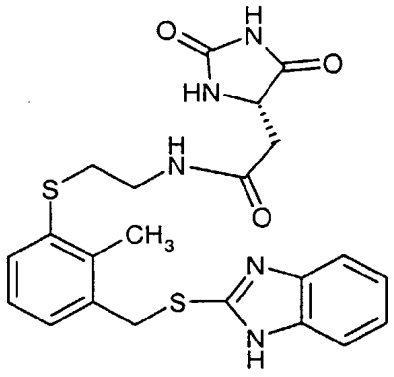
Compound 40



Mass spec' molecular ion: M+H= 440

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]cyclohexanecarboxamide

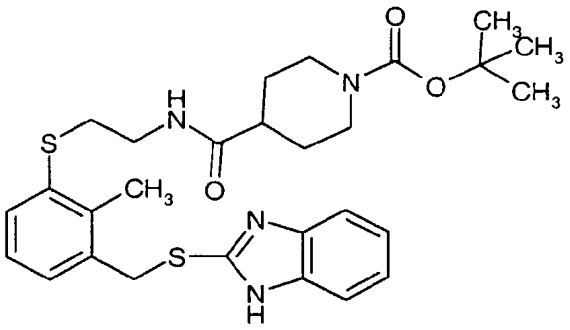
Compound 41



Mass spec' molecular ion: M+H= 470

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-[(4*S*)-2,5-dioxoimidazolidinyl]acetamide

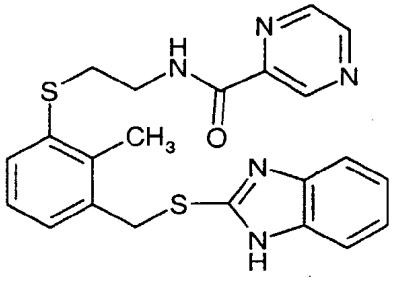
Compound 42



Mass spec' molecular ion: M+H= 541

tert-butyl 4-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]amino}carbonyl)-1-piperidinecarboxylate

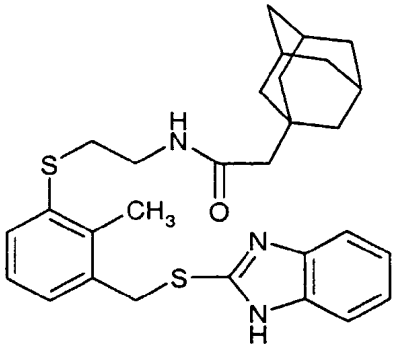
Compound 43



Mass spec' molecular ion: M+H= 436

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-pyrazinecarboxamide

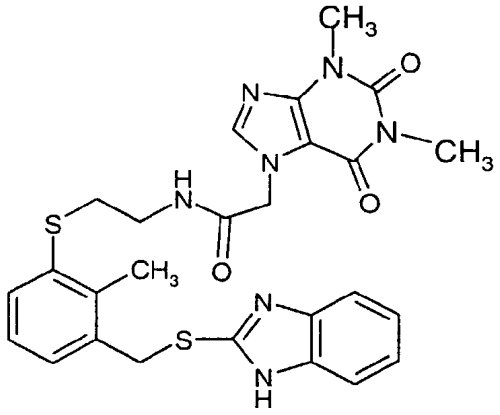
Compound 44



Mass spec' molecular ion: M+H= 506

2-(1-adamantyl)-*N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]acetamide

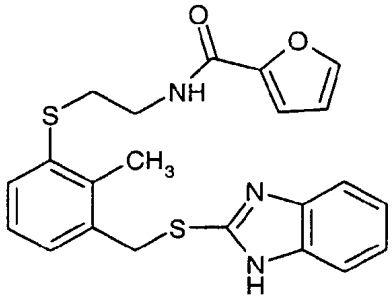
Compound 45



Mass spec' molecular ion: M+H= 550

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)acetamide

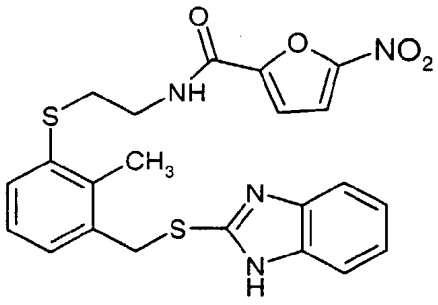
Compound 46



Mass spec' molecular ion: M+H= 424

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-furamide

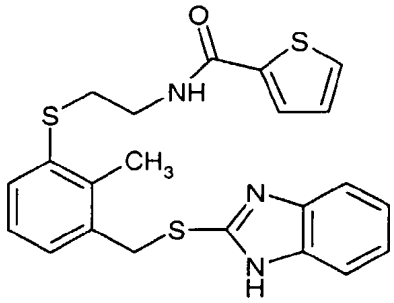
Compound 47



Mass spec' molecular ion: M+H= 469

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-5-nitro-2-furamide

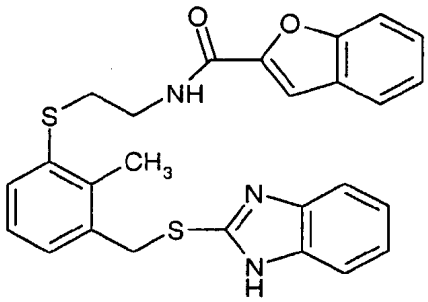
Compound 48



Mass spec' molecular ion: M+H= 440

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-thiophenecarboxamide

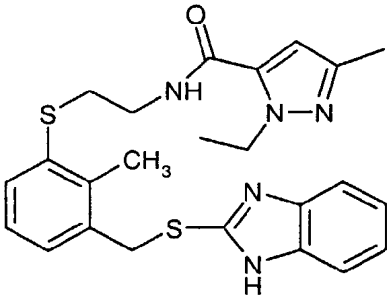
Compound 49



Mass spec' molecular ion: M+H= 474

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-1-benzofuran-2-carboxamide

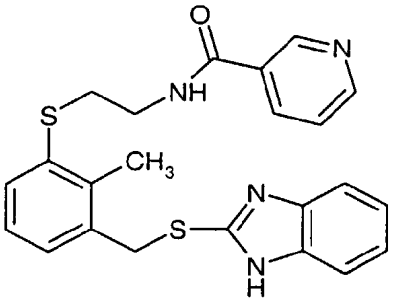
Compound 50



Mass spec' molecular ion: M+H= 466

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide

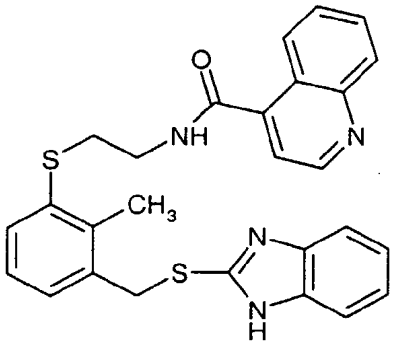
Compound 51



Mass spec' molecular ion: M+H= 435

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]nicotinamide

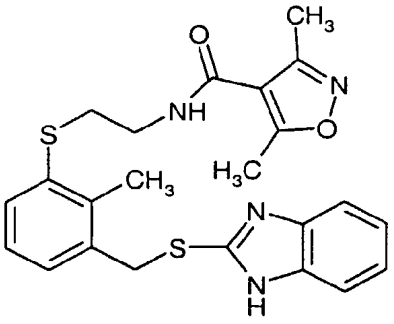
Compound 52



Mass spec' molecular ion: M+H= 485

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-4-quinolinecarboxamide

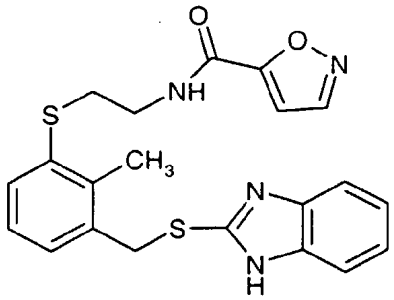
Compound 53



Mass spec' molecular ion: M+H= 453

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-3,5-dimethyl-4-isoxazolecarboxamide

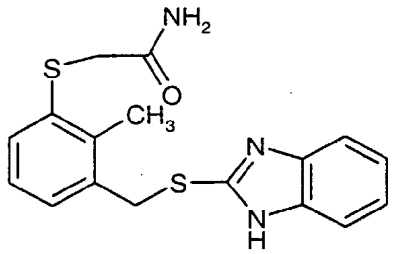
Compound 54



Mass spec' molecular ion: M+H= 425

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-5-isoxazolecarboxamide

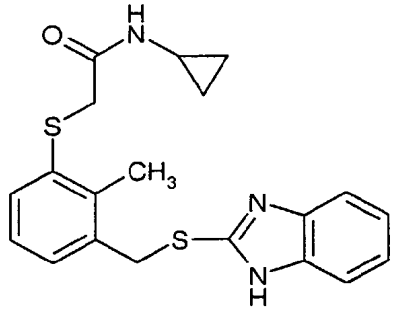
Compound 55



Mass spec' molecular ion: M+H= 344

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetamide

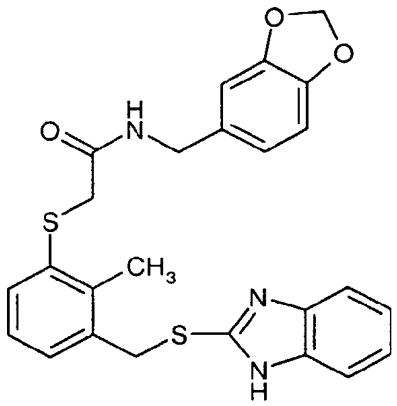
Compound 56



Mass spec' molecular ion: M+H= 384

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclopropylacetamide

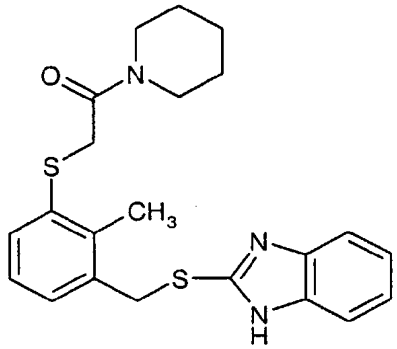
Compound 57



Mass spec' molecular ion: M+H= 478

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(1,3-benzodioxol-5-ylmethyl)acetamide

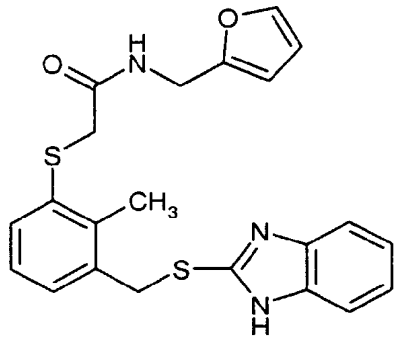
Compound 58



Mass spec' molecular ion: M+H= 412

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(1-piperidinyl)-1-ethanone

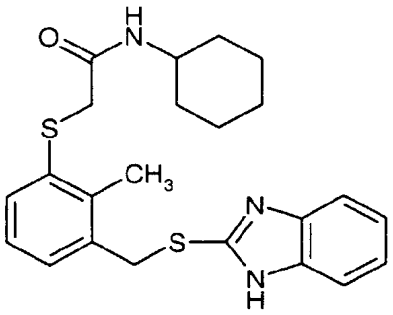
Compound 59



Mass spec' molecular ion: M+H= 424

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2-furylmethyl)acetamide

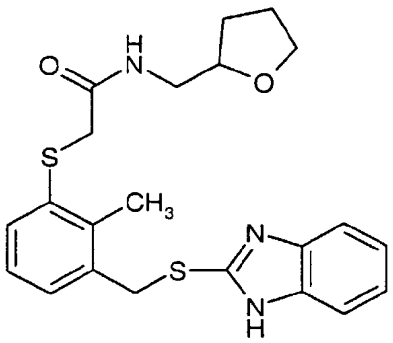
Compound 60



Mass spec' molecular ion: M+H= 426

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclohexylacetamide

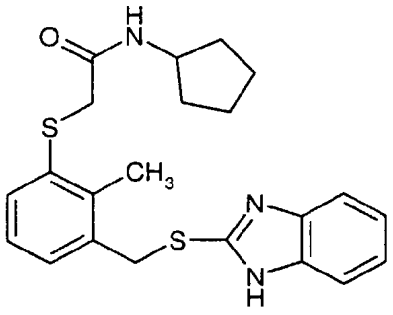
Compound 61



Mass spec' molecular ion: M+H= 428

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(tetrahydro-2-furanylmethyl)acetamide

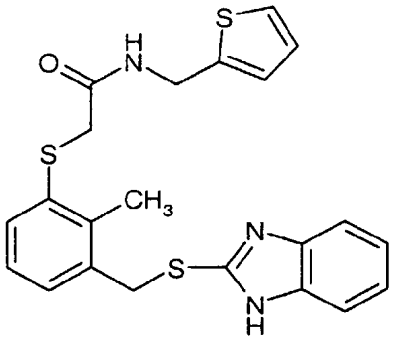
Compound 62



Mass spec' molecular ion: M+H= 412

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclopentylacetamide

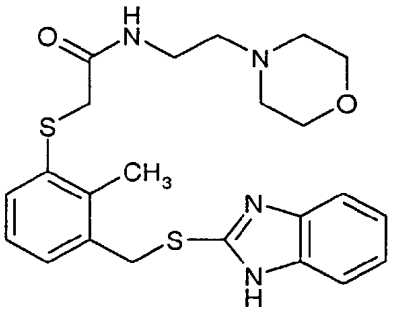
Compound 63



Mass spec' molecular ion: M+H= 440

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2-thienylmethyl)acetamide

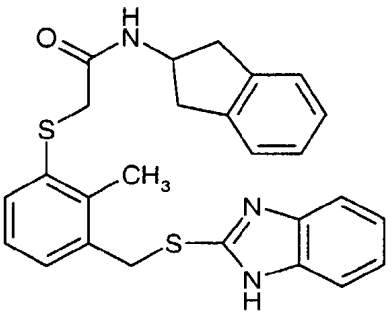
Compound 64



Mass spec' molecular ion: M+H= 457

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(4-morpholinyl)ethyl]acetamide

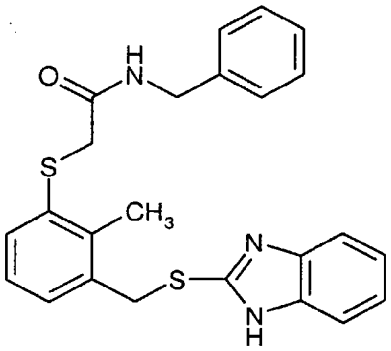
Compound 65



Mass spec' molecular ion: M+H= 460

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)acetamide

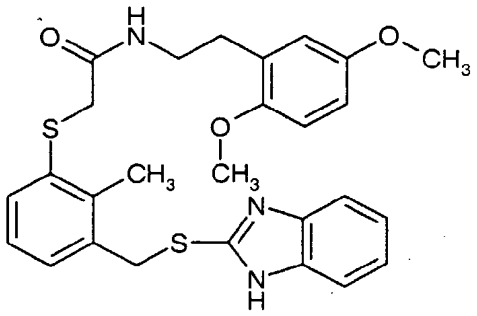
Compound 66



Mass spec' molecular ion: M+H= 434

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-benzylacetamide

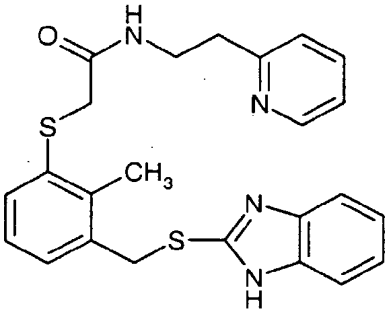
Compound 67



Mass spec' molecular ion: M+H= 508

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2,5-dimethoxyphenethyl)acetamide

Compound 68

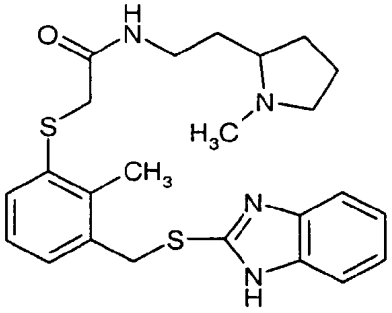


NMR:

^{1}H NMR (dmso-*d*6) ppm 2.42 (s, 3H), 2.71 (m, 2H), 3.77 (s, 2H), 4.37 (m, 2H), 4.62 (s, 2H), 7.10-7.16 (m, 7H), 7.56 (m, 1H), 7.66 (m, 1H), 8.49 (m, 1H), 8.75 (m, 1H), 12.61 (s, 1H, N*H*).

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(2-pyridinyl)ethyl]acetamide

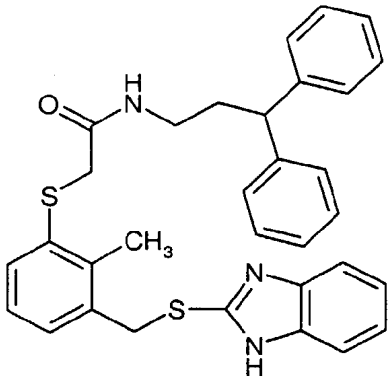
Compound 69



Mass spec' molecular ion: M+H= 455

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(1-methyl-2-pyrrolidinyl)ethyl]acetamide

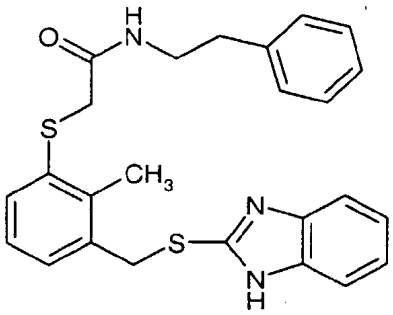
Compound 70



Mass spec' molecular ion: M+H= 538

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(3,3-diphenylpropyl)acetamide

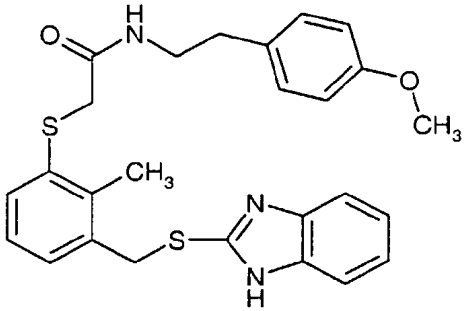
Compound 71



Mass spec' molecular ion: M+H= 449

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-phenethylacetamide

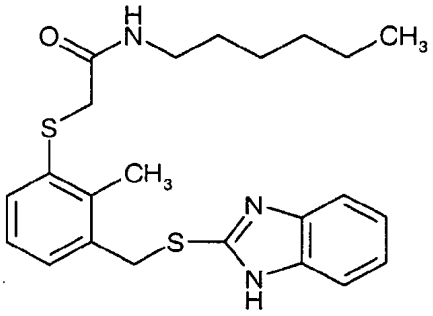
Compound 72



Mass spec' molecular ion: M+H= 479

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-methoxyphenethyl)acetamide

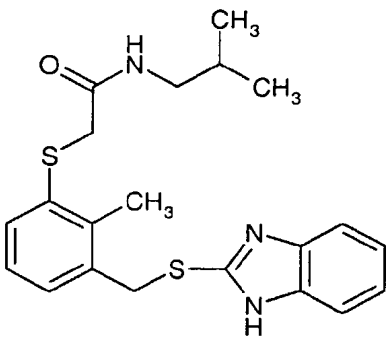
Compound 73



Mass spec' molecular ion: M+H= 429

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-hexylacetamide

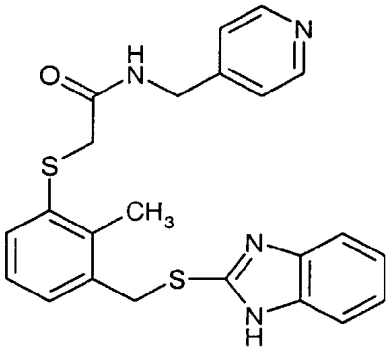
Compound 74



Mass spec' molecular ion: M+H= 401

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-isobutylacetamide

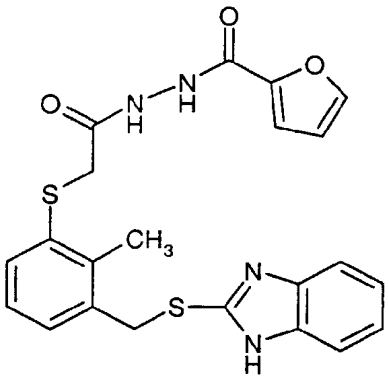
Compound 75



Mass spec' molecular ion: M+H= 436

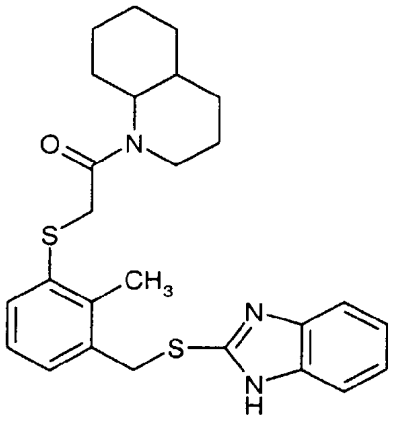
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-pyridinylmethyl)acetamide

Compound 76



N'-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetyl]-2-furohydrazide

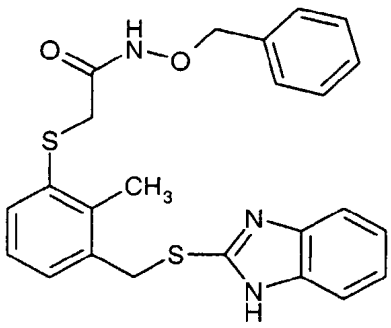
Compound 77



Mass spec' molecular ion: M+H= 467

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-octahydro-1(2*H*)-quinolinyl-1-ethanone

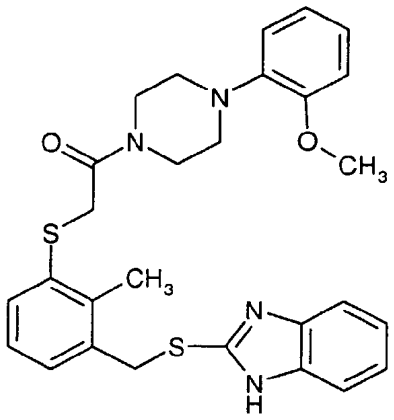
Compound 78



Mass spec' molecular ion: M+H= 450

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(benzyloxy)acetamide

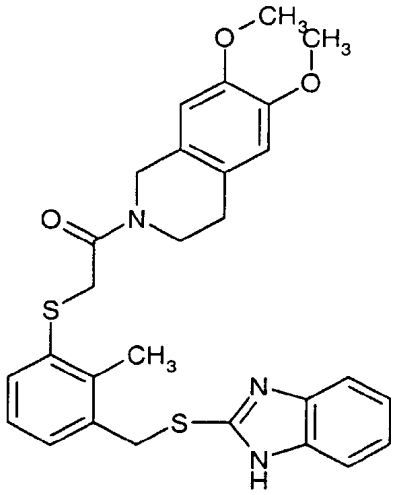
Compound 79



Mass spec' molecular ion: M+H= 519

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-[4-(2-methoxyphenyl)-1-piperazinyl]-1-ethanone

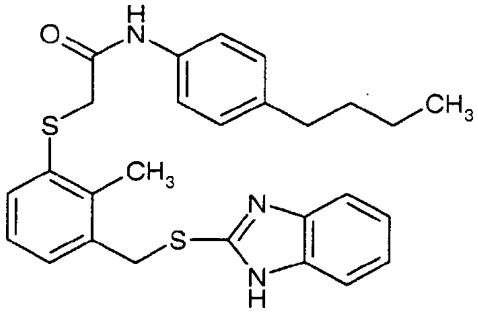
Compound 80



Mass spec' molecular ion: M+H= 521

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-[6,7-dimethoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-1-ethanone

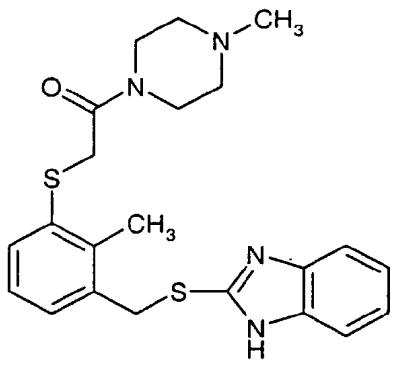
Compound 81



Mass spec' molecular ion: M+H= 477

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-butylphenyl)acetamide

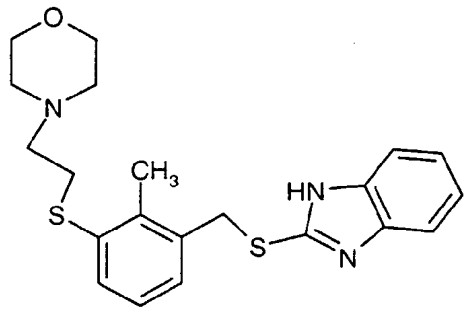
Compound 82



Mass spec' molecular ion: M+H= 427

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(4-methyl-1-piperazinyl)-1-ethanone

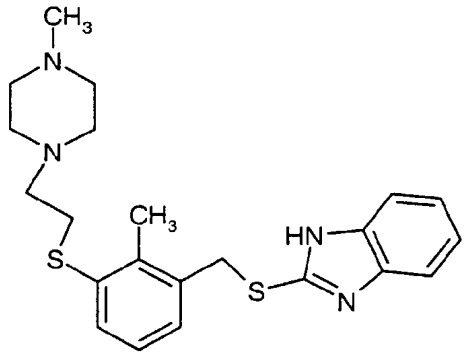
Compound 83



Mass spec' molecular ion: M+H= 400

2-[(2-methyl-3-{[2-(4-morpholinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

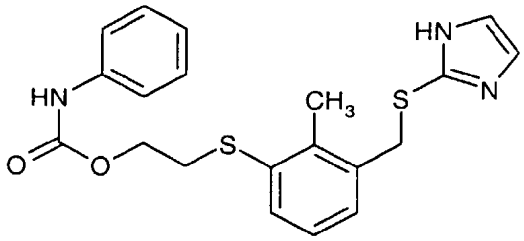
Compound 84



Mass spec' molecular ion: M+H= 413

2-[(2-methyl-3-{[2-(4-methyl-1-piperazinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

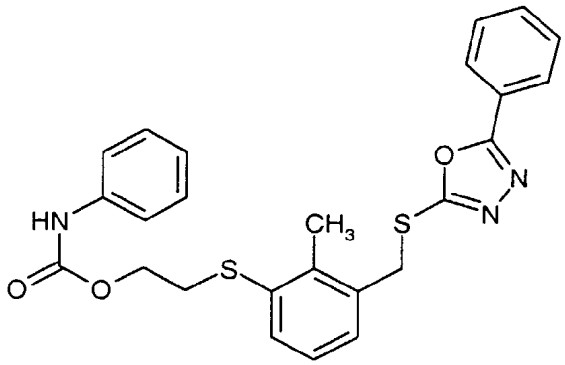
Compound 85



Mass spec' molecular ion: M+H= 400

2-({3-[(1*H*-imidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate

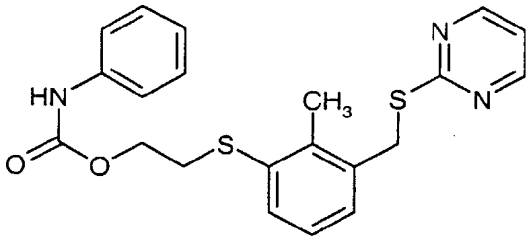
Compound 86



Mass spec' molecular ion: M+H= 478

2-[(2-methyl-3-{[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate

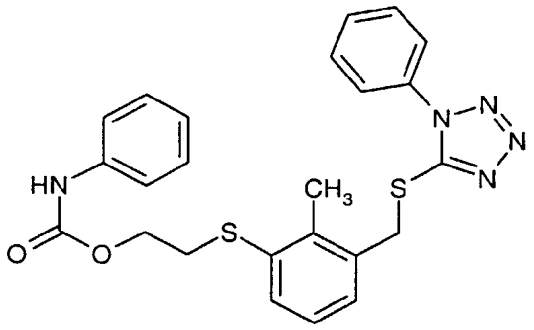
Compound 87



Mass spec' molecular ion: M+H= 412

2-({2-methyl-3-[(2-pyrimidinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate

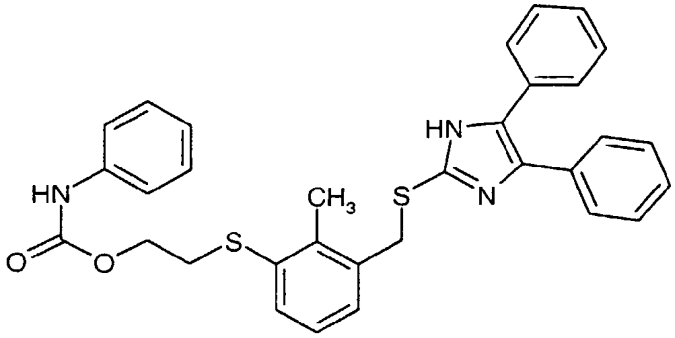
Compound 88



Mass spec' molecular ion: M+H= 478

2-[(2-methyl-3-{[(1-phenyl-1*H*-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate

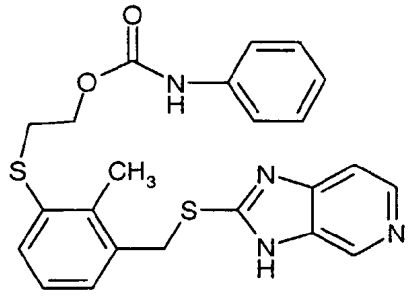
Compound 89



Mass spec' molecular ion: M+H= 552

2-[(3-{[(4,5-diphenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-2-methylphenyl)sulfanyl]ethyl phenylcarbamate

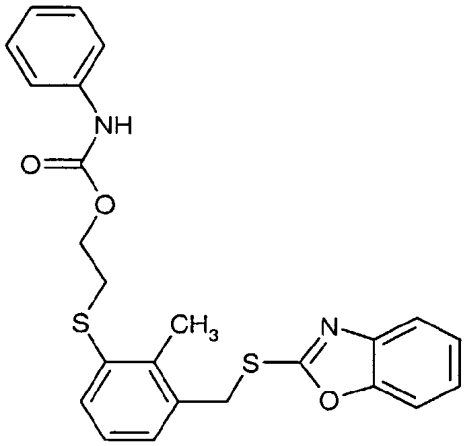
Compound 90



Mass spec' molecular ion: M+H= 451

2-({3-[(3*H*-imidazo[4,5-*c*]pyridin-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate

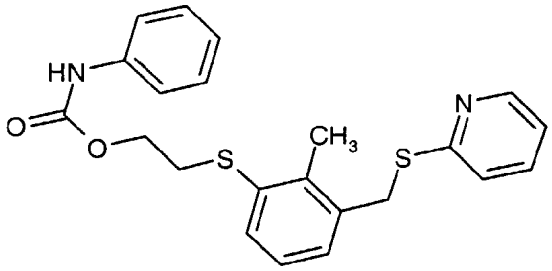
Compound 91



Mass spec' molecular ion: M+H= 451

2-({3-[(1,3-benzoxazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate

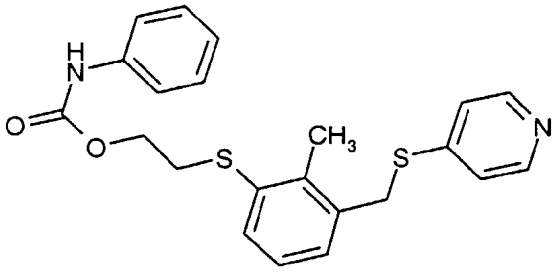
Compound 92



Mass spec' molecular ion: M+H= 411

2-({2-methyl-3-[(2-pyridinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate

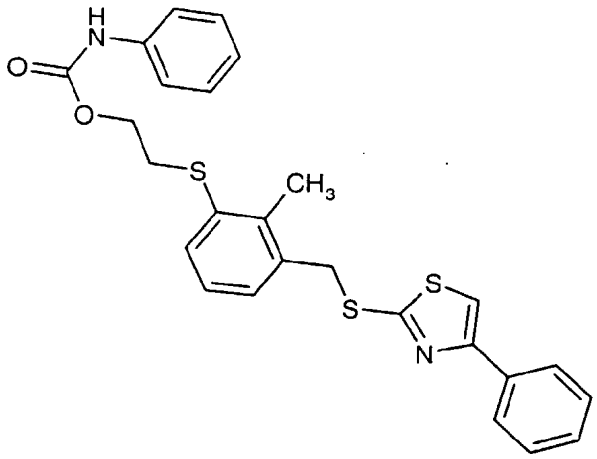
Compound 93



Mass spec' molecular ion: M+H= 411

2-({2-methyl-3-[(4-pyridinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate

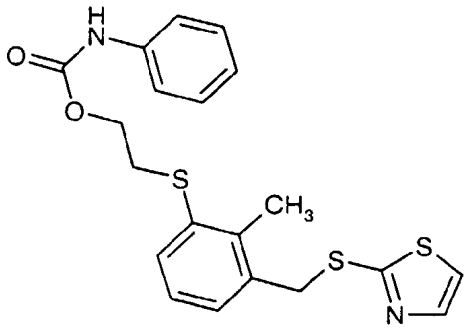
Compound 94



Mass spec' molecular ion: M+H= 493

2-[(2-methyl-3-{[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate

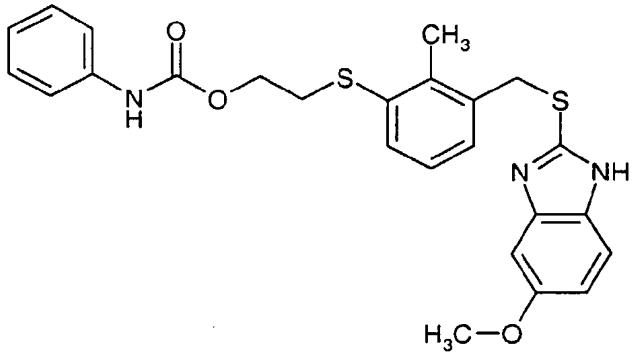
Compound 95



Mass spec' molecular ion: M+H= 417

2-({2-methyl-3-[(1,3-thiazol-2-ylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate

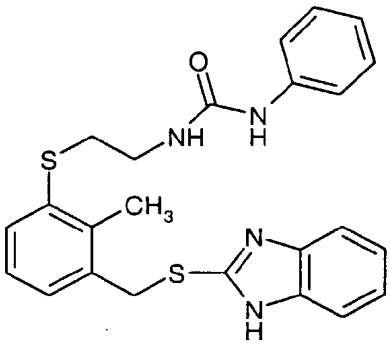
Compound 96



Mass spec' molecular ion: M+H= 480

2-[(3-{[(5-methoxy-1*H*-benzimidazol-2-yl)sulfanyl]methyl}-2-methylphenyl)sulfanyl]ethyl phenylcarbamate

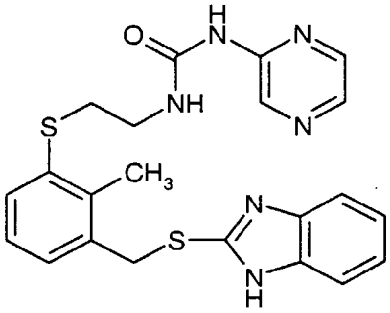
Compound 97



Mass spec' molecular ion: M+H= 449

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-phenylurea

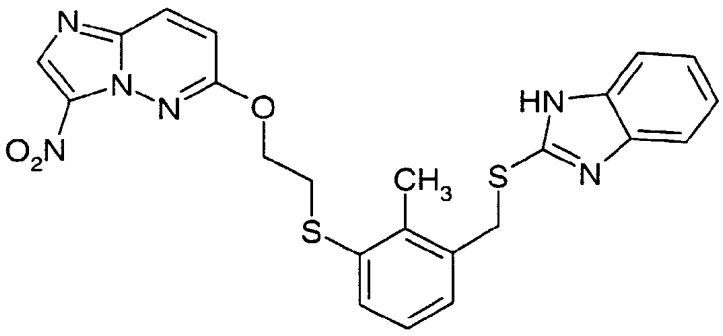
Compound 98



Mass spec' molecular ion: M+H= 451

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-(2-pyrazinyl)urea

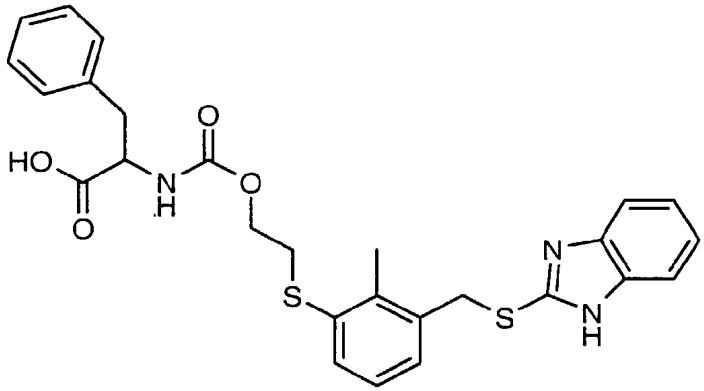
Compound 99



Mass spec' molecular ion: M+H= 493

6-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]-3-nitroimidazo[1,2-*b*]pyridazine

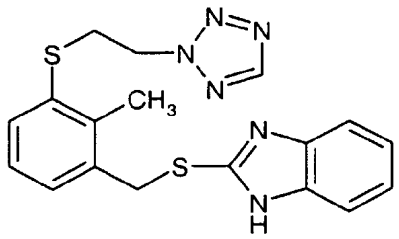
Compound 100



Mass spec' molecular ion: M+H= 522

N-{[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}phenylalanine

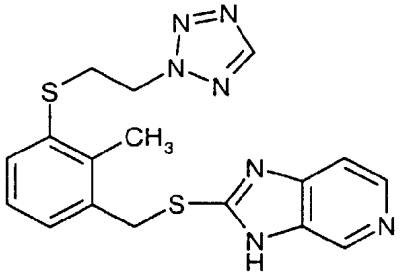
Compound 101



Mass spec' molecular ion: M+H= 383

2-[(2-methyl-3-{[2-(2*H*-1,2,3,4-tetrazol-2-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

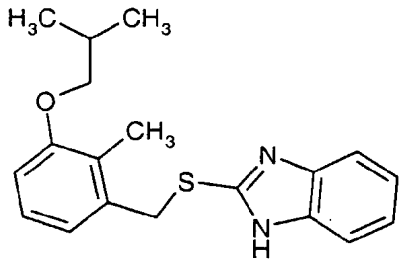
Compound 102



Mass spec' molecular ion: M+H= 384

2-[(2-methyl-3-{[2-(2*H*-1,2,3,4-tetrazol-2-yl)ethyl]sulfanyl}benzyl)sulfanyl]-3*H*-imidazo[4,5-*c*]pyridine

Compound 103

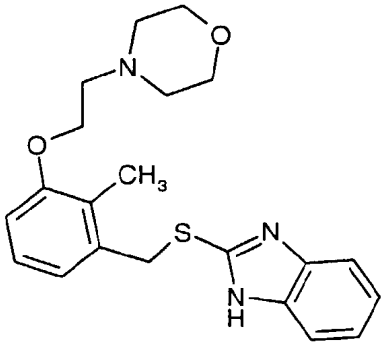


NMR:

400 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 1.03 (d, 6H), 2.10 (m, 1H), 2.29 (s, 3H), 3.70 (d, 2H), 4.56 (s, 2H), 6.75 (d, 1H), 6.90 (d, 1H), 7.05 (t, 1H), 7.20 (t, 1H), 7.21 (t, 1H), 7.29 (d, 1H), 7.70 (d, 1H).

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole

Compound 104

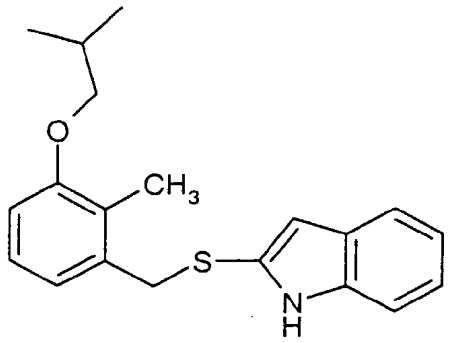


NMR:

500 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 2.30 (s, 3H), 2.65 (m, 4H), 2.87 (m, 2H), 3.75 (m, 4H), 4.13 (m, 2H), 4.60 (s, 2H), 6.80 (d, 1H), 6.97 (d, 1H), 7.09 (t, 1H), 7.19-7.30 (m, 2H), 7.33 (d, 1H), 7.74 (d, 1H).

2-({2-methyl-3-[2-(4-morpholinyl)ethoxy]benzyl}sulfanyl)-1*H*-benzimidazole

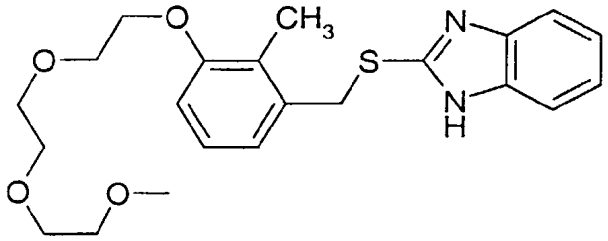
Compound 105



Mass spec' molecular ion: [M-H]= 324

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-indole

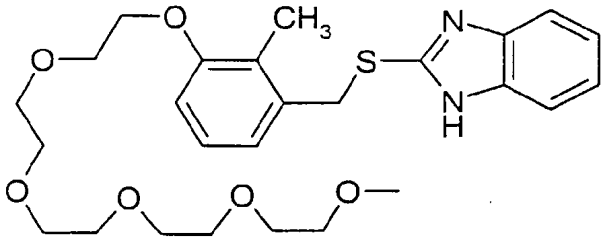
Compound 106



Mass spec' molecular ion: M+Na= 439

2-[(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole

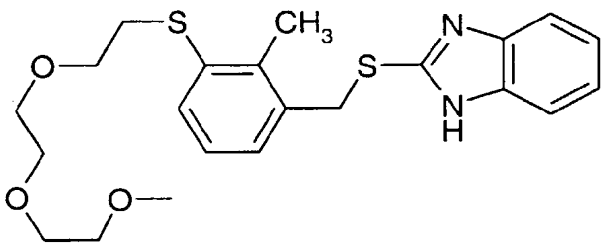
Compound 107



Mass spec' molecular ion: M+Na = 527

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-yloxy)benzyl]sulfanyl}-1*H*-benzimidazole

Compound 108

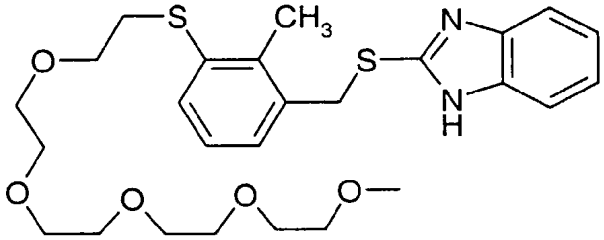


NMR:

500 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 2.43 (s, 3H), 3.02 (t, 2H), 3.35 (s, 3H), 3.52-3.55 (m, 2H), 3.56-3.68 (m, 8H), 4.55 (s, 2H), 7.01 (t, 1H), 7.12 (d, 1H), 7.19-7.23 (m, 2H), 7.25 (d, 1H), 7.50-7.55 (m, 2H).

2-{[3-({2-[2-(2-methoxyethoxy)ethoxy]ethyl}sulfanyl)-2-methylbenzyl]sulfanyl}-1*H*-benzimidazole

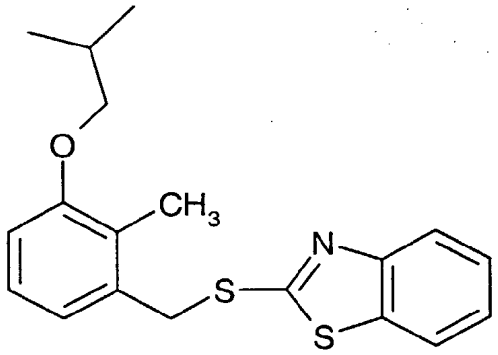
Compound 109



Mass spec' molecular ion: M+Na= 543

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazole

Compound 110

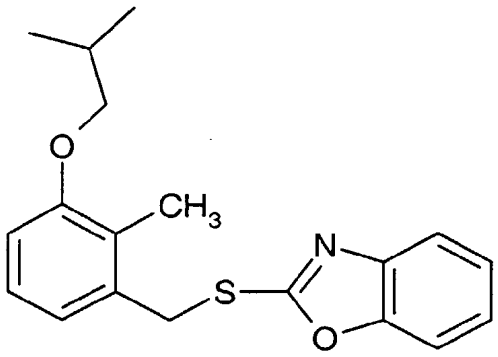


NMR:

600 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 1.05 (d, 3H), 1.06 (d, 3H), 2.15 (m, 1H), 2.34 (s, 3H), 3.73 (d, 2H), 4.65 (s, 2H), 6.79 (d, 1H), 7.02 (d, 1H), 7.11 (t, 1H), 7.31 (t, 1H), 7.44 (t, 1H), 7.77 (d, 1H), 7.92 (d, 1H).

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1,3-benzothiazole

Compound 111

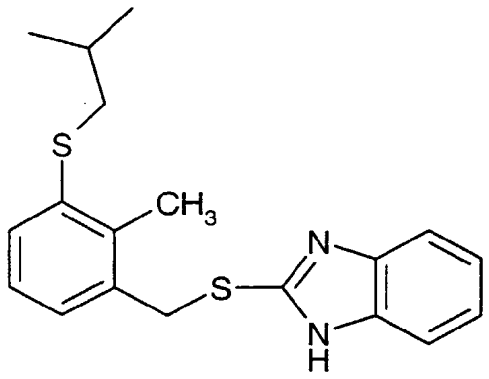


NMR:

600 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 1.10 (d, 6H), 2.16 (m, 1H), 2.39 (s, 3H), 3.76 (d, 2H), 4.66 (s, 2H), 6.83 (d, 1H), 7.07 (d, 1H), 7.15 (t, 1H), 7.28 (t, 1H), 7.32 (t, 1H), 7.47 (d, 1H), 7.68 (d, 1H).

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1,3-benzoxazole

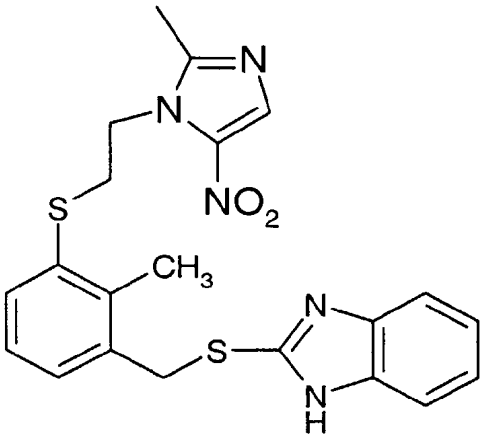
Compound 112



Mass spec' molecular ion: M+H= 343

2-{[3-(isobutylsulfanyl)-2-methylbenzyl]sulfanyl}-1*H*-benzimidazole

Compound 113

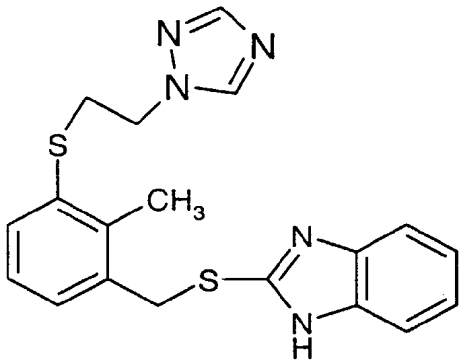


NMR:

300 MHz ^{1}H-NMR (CH_3OH-*d*4) ppm 2.26 (s, 3H), 2.43 (s, 3H), 3.29 (t, 2H), 4.40 (t, 2H), 4.49 (s, 2H), 4.89 (broad, >3H, exchangeable with D_2O), 7.02 (t, 1H), 7.09-7.19 (m, 3H), 7.29 (d, 1H), 7.36-7.49 (m, 2H), 7.79 (s, 1H).

2-[(2-methyl-3-{[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

Compound 114

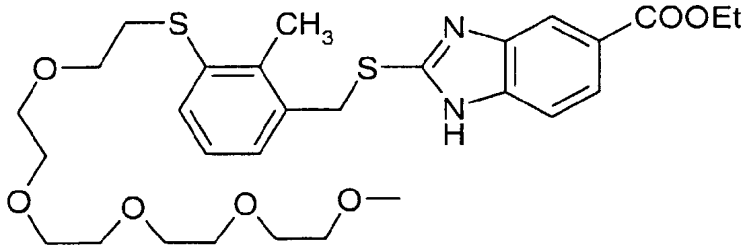


NMR:

300 MHz ^{1}H-NMR ($CHCl_3$-*d*) ppm 2.37 (s, 3H), 3.28 (t, 2H), 4.30 (t, 2H), 4.43 (s, 2H), 6.86-7.00 (m, 2H), 7.10-7.22 (m, 3H), 7.32-7.72 (broad, 2H), 7.87 (s, 1H), 7.91 (s, 1H).

2-[(2-methyl-3-{[2-(1*H*-1,2,4-triazol-1-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

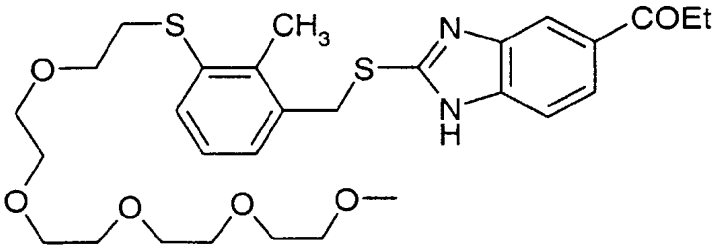
Compound 115



Mass spec' molecular ion: M+H= 593

ethyl 2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazole-5-carboxylate

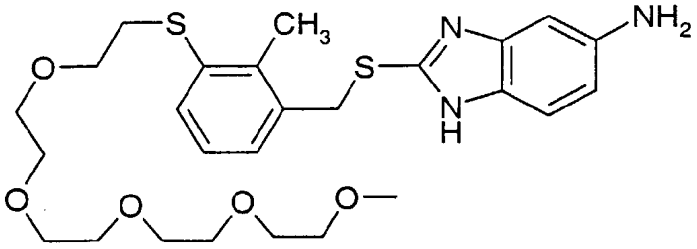
Compound 116



Mass spec' molecular ion: M+Na= 599

1-(2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-yl)-1-propanone

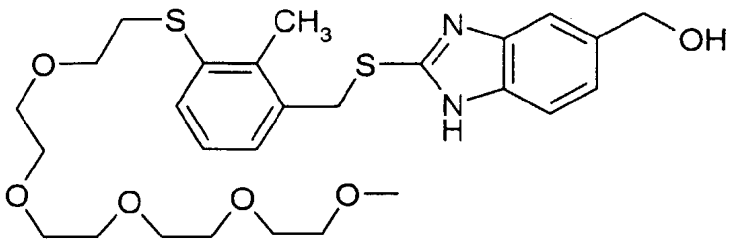
Compound 117



Mass spec' molecular ion: M+Na= 558

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-amine

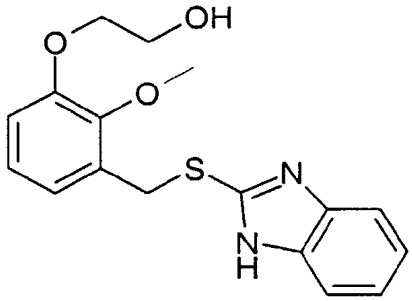
Compound 118



Mass spec' molecular ion: M+Na= 573

(2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-yl)methanol

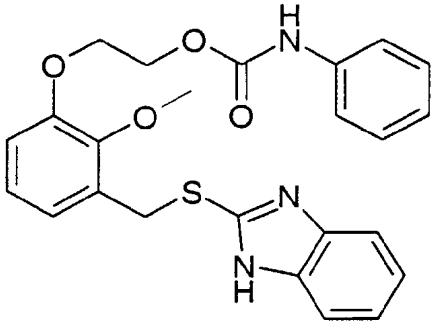
Compound 119



Mass spec' molecular ion: Mass spec' molecular ion: [M-H]- = 329

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methoxyphenoxy}-1-ethanol

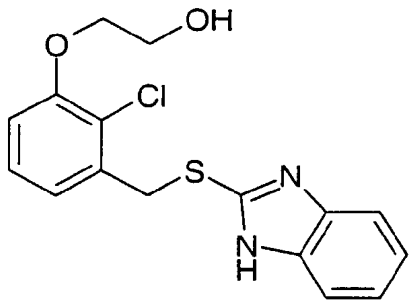
Compound 120



Mass spec' molecular ion: M+H= 450

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methoxyphenoxy}ethyl phenylcarbamate

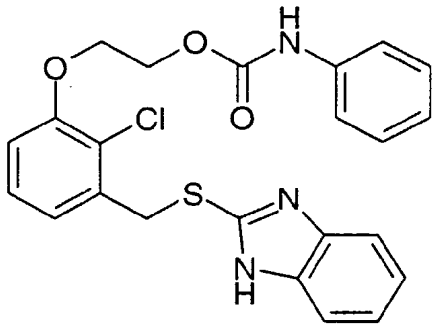
Compound 121



Mass spec' molecular ion: M+H= 335

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}-1-ethanol

Compound 122



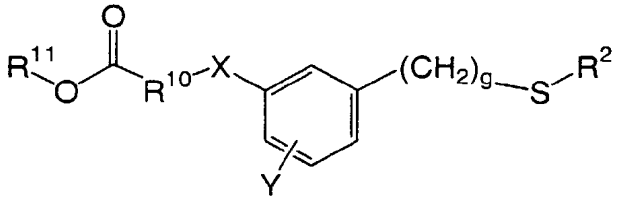
Mass spec' molecular ion: M+H= 454

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}ethyl phenylcarbamate

The compounds of formula I above may be converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate, or an alkali metal salt such as a sodium or potassium salt.

The compounds of formula I can be prepared by a process comprising any one of steps (a) to (h) as follows:

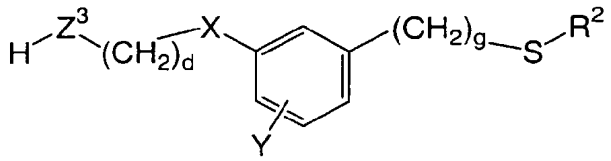
(a) reducing compound VI



VI

wherein R^{10} represents $(CH_2)_d$ or $-(CH_2)_{f-1}-O-(CH_2)_e-$ and R^{11} represents H or C_{1-6}alkyl; or

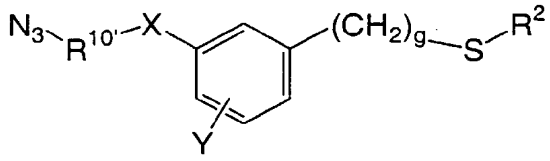
(b) reacting compound VII with R^6-NCO



VII

wherein Z^3 represents O or NH; or

(c) reducing compound VIII

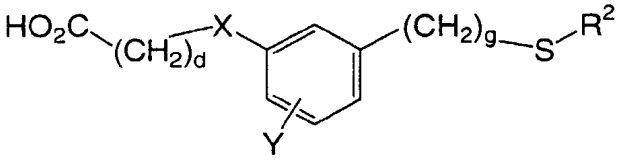


VIII

wherein $R^{10'}$ represents a bond, $(CH_2)_d$ or $-(CH_2)_f$-O-$(CH_2)_e$-; or

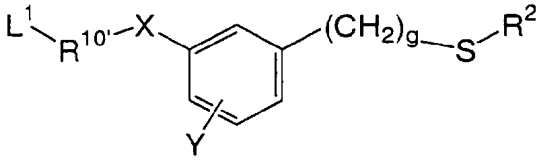
(d) reacting compound VII with R^6-COOH; or

(e) reacting compound IX with NHR^4R^5; or



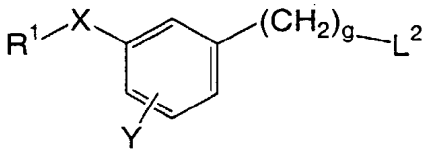
IX

(f) reacting compound X with NHR^4R^5



X

wherein L^1 represents a leaving group and $R^{10'}$ represents $(CH_2)_d$ or $-(CH_2)_f$-O-$(CH_2)_e$-; or

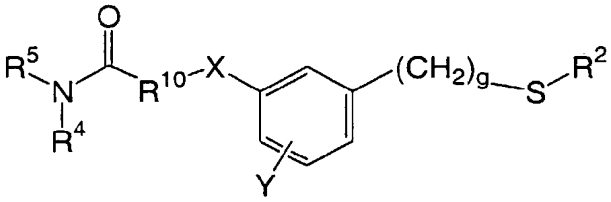


XI

(g) reacting compound XI with R^2-SH

wherein L^2 represents a leaving group; or

(h) reducing compound XII



XII

wherein R^{10} represents $(CH_2)_d$ or $-(CH_2)_{f-1}$-O-$(CH_2)_e$-.

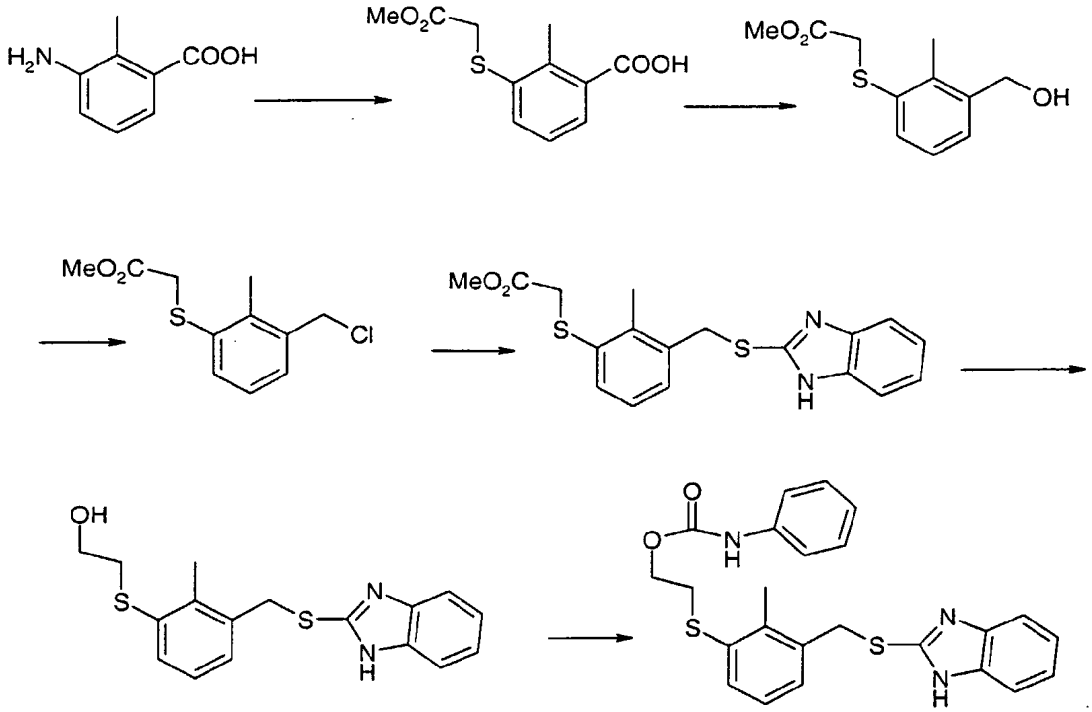
It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of the present invention have anti-*Helicobacter pylori* activity, i.e., they can be administered to a mammalian patient therapeutically to treat *Helicobacter pylori* infection in the patient and/or to prevent such infection. A further advantage of compounds of the invention is that they are particularly selective for *Helicobacter pylori*.

Experimental

Scheme 1



3-[(2-Methoxy-2-oxoethyl)sulfanyl]-2-methylbenzoic acid

3-amino-2-methylbenzoic acid, 11.3 g, was dissolved in H_2O (100 mL) and conc. HCL (15 mL) was added at 0 °C $NaNO_2$ (5.5 g) in H_2O (40 mL) was added to the above

suspension over 30min. The above diazonium salt was kept at 0°C and added slowly (over 40 min) to a solution of methyl thioglycolate, 8.48 g in 50 mL of MeOH at 60 °C. During the addition, the pH of the reaction medium was kept around 5 ~ 6 by adding sat. Na_2CO_3 very carefully. After the end of addition, the reaction was heated at 60 to 70 °C for additional 45min. The mixture was cooled to 0 °C and pH was adjusted to ~ 1 with conc. HCL & extracted with EtOAc, dried over Na_2SO_4, filtered, and the solvent was evaporated to give 17.4 g of crude 3-[(2-methoxy-2-oxoethyl)sulfanyl]-2-methylbenzoic acid.

Methyl 2-{[3-(hydroxymethyl)-2-methylphenyl]sulfanyl}acetate

3-[(2-methoxy-2-oxoethyl)sulfanyl]-2-methylbenzoic acid, 15.4 g, was dissolved in 120 mL THF and cooled on an ice bath. Borane-THF solution, 130 mL (1M in THF) was added slowly. The reaction was stirred for 1 hour then quenched with ice water, extracted with EtOAc, dried over Na_2SO_4, purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc = 20/1) to give 5 grams of methyl 2-{[3-(hydroxymethyl)-2-methylphenyl]sulfanyl}acetate.

Methyl 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}acetate

Methyl 2-{[3-(hydroxymethyl)-2-methylphenyl]sulfanyl}acetate, 4.4 g was dissolved in 220 mL methylene chloride, treated with thionyl chloride, 5 mL, and stirred at room temp. for 4 hours. The solvents were evaporated to yield 4.3 g of methyl 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}acetate as a slightly brown oil.

Methyl 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetate

2-mercaptobenzimidazole, 2 g, was dissolved in a solution of 10 mL water, 30 mL methanol, and 0.53 g NaOH, and cooled on an ice bath. A solution of 3.2 g of methyl 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}acetate in 50 mL methanol was added and the reaction was stirred at room temp. for 6 hours. The solvents were evaporated and the residue was partitioned between 600 mL CH_2Cl_2 and 300 mL of 5% Na_2CO_3, the org. layer was collected, dried over Na_2SO_4 and evaporated to give 3.1 g methyl 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetate as a light yellow solid.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol

Methyl 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetate, 5.7 g, was dissolved in 100 mL THF and cooled on a ice-bath. Lithium aluminum hydride, 0.5 g was added portion-wise under ca 5 min. After 30 min the reaction was quenched with Glauber salt($Na_2SO_4x10H_2O$). Filtration and evaporation afforded 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol, 4.1 g.

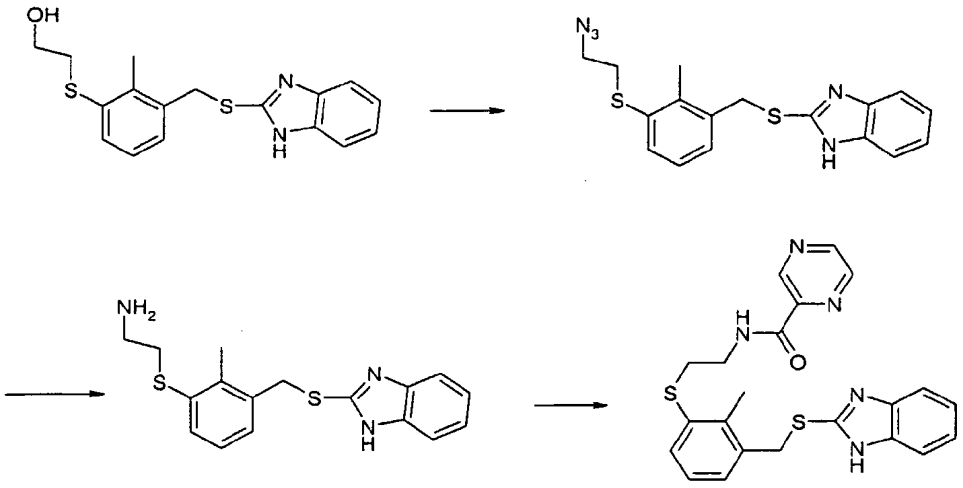
Mass spec.; M+H=331.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate

100 mg of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol was dissolved in 2 mL DMF, and 35 mg phenyl isocyanate was added, the mixture was stirred for 18 hours at room temp., and concentrated in vacuo. Purification by reverse phase HPLC gave 60 mg 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}-sulfanyl)ethyl phenylcarbamate as a white solid.

Mass spec.; M+H=450.

Scheme 2



2-({3-[(2-Azidoethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol, 0.165 g, triphenylphosphine, 0.184 g, and sodium azide, 0.13 g, were combined with stirring in 4 mL DMF on an ice bath, carbon tetrabromide, 0.25 g, was added, and the reaction was allowed to proceed for 18 hours. 20 mL methylene chloride was added, the resulting suspension was filtered, the solids were rinsed with methylene chloride and the filtrate washed with brine, dried over Na_2SO_4, and evaporated. Purification of the residue by flash chromatography (silica gel, EtOAc/Hexane = 1:5) gave 2-({3-[(2-azidoethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole, 0.85 g. Mass spec.; M+H=356

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine

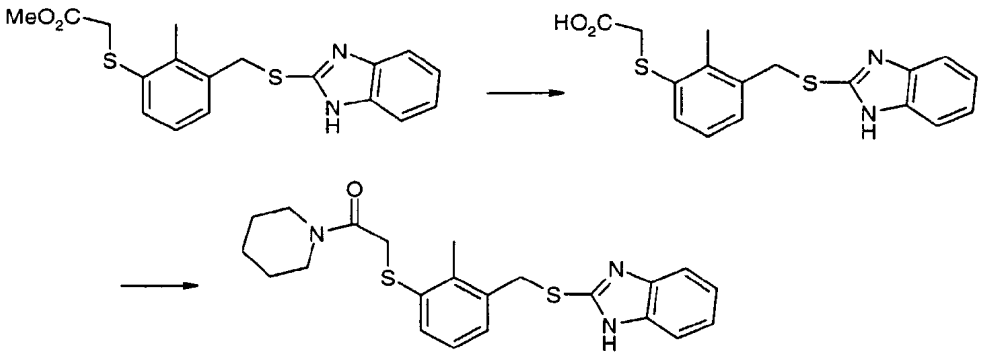
2-({3-[(2-azidoethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole, 0.42 g, was added to a suspension of 0.3 g lithium aluminum hydride in 10 mL THF over an ice bath. After 45 minutes, the reaction was quenched with $Na_2SO_4.10H_2O$ until H_2 evolution ceased.

The mixture was filtered, evaporated, dissolved in ethyl acetate and extracted with 1N HCl. The aqueous layer was washed with ethyl acetate and evaporated to give 275 mg of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine as a white solid. Mass spec.; M+H=330

***N*-[2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-pyrazinecarboxamide**

To a solution of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine (658 mg), 2-pyrazinecarboxylic acid (248 mg), diisopropylethylamine (1 mL) and DMF (8 mL) was added HBTU (829 mg). The resulting mixture was stirred overnight. The mixture was transferred to a sep. funnel and diluted with EtOAc (200 mL) and washed with water (2 x 100 mL). The organic layer was washed with Sat. Brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by reverse phase HPLC, C18 column (10-100% MeCN/H_2O) to give *N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-pyrazinecarboxamide as 600mg white solid. Mass spec.; M+H=436

Scheme 3



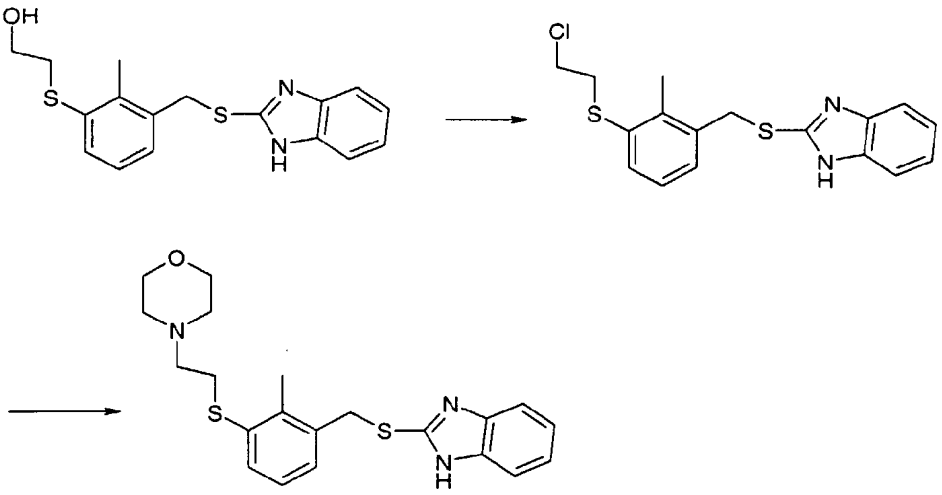
2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetic acid

Methyl 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetate, 0.68 g, was dissolved in 14 mL MeOH and treated with excess LiOH dissolved in 2 mL H_2O for 1 h. The solvents were evaporated and the residue was partitioned between 100 mL 5% Na_2CO_3 and 100 mL EtOAc. The aq layer was collected and the pH was adjusted to about 4 with 4M HCl. The aq layer was extracted with a 2:1 ethyl acetate/THF mixture. The combined organic layers were dried over $MgSO_4$ and evaporated to leave 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetic acid as a white solid, 0.5 g.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(1-piperidinyl)-1-ethanone

100 mg of 2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetic acid was dissolved in 2 mL of DMF, 30 mg piperidine and 120 mg of HBTU were added. The mixture was stirred for 18 hours, diluted with ethyl acetate, washed with 5% $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to give 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(1-piperidinyl)-1-ethanone, 110 mg. Mass spec.; M+H=412.

Scheme 4



2-({3-[(2-Chloroethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole

0.38 g 2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol was combined with 5 mL CH_2Cl_2 and cooled to 0 °C. Excess $SOCl_2$ was added. Cold bath removed. Suspension stirred at RT for 2 hours. Concentrated in vacuo, 0.39 g crude 2-({3-[(2-chloroethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole obtained.

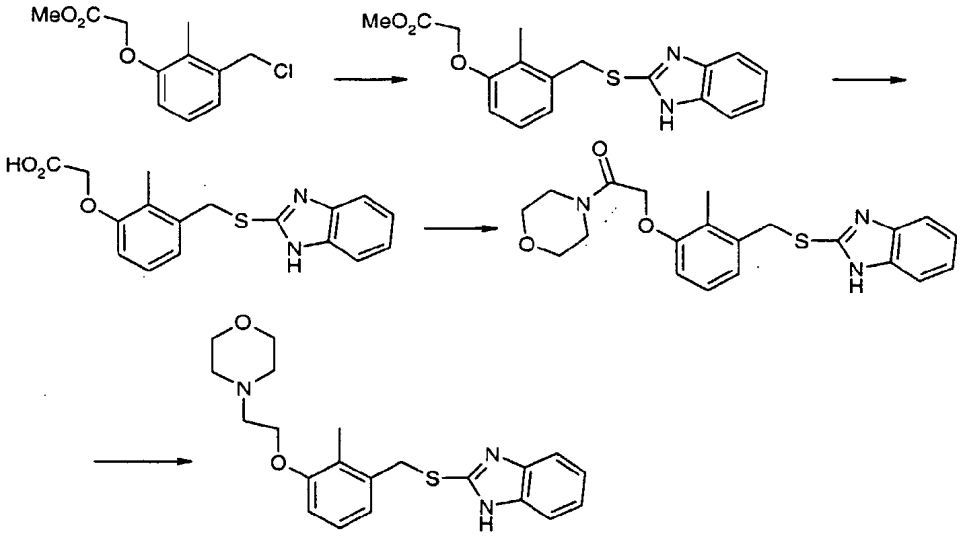
2-[(2-methyl-3-{[2-(4-morpholinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole

2-({3-[(2-Chloroethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole, 0.202 g, 1.3 mL morpholine, 3 mL DMF, and 1 mL DMSO combined and warmed at 80 °C for 1 day. Diluted to 100 mL with ethyl acetate. Washed with water, brine (2X), dried over $MgSO_4$, evaporated to give a thick oil. Purified via preparative HPLC to give 2-[(2-methyl-3-{[2-(4-morpholinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole as a fine powder, 0.12 g. Mass spec.; M+H=400.

Compound 113 can be prepared by a similar scheme by using 2-methyl-5-nitro-1*H*-imidazole in place of morpholine.

Compound 114 can be prepared by a similar scheme by using 1*H*-triazole in place of morpholine.

Scheme 5



Methyl 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetate

2-Mercaptobenzimidazole, 2 g, was dissolved in a solution of 10 mL water, 30 mL methanol, and 0.53 g NaOH, and cooled on an ice bath. A solution of 3.2 g of methyl 2-[3-(chloromethyl)-2-methylphenoxy]acetate in 50 mL methanol was added and the reaction was stirred at room temp. for 6 hours. The solvents were evaporated and the residue was partitioned between 600 mL CH_2Cl_2 and 300 mL of 5% Na_2CO_3, the org. layer was collected, dried over Na_2SO_4 and evaporated to give 3.1 g methyl 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetate as a light yellow solid.

2-{3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetic acid

Methyl 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetate, 0.68 g, was dissolved in 14 mL MeOH and treated with excess LiOH dissolved in 2 mL H_2O for 1 h. The solvents were evaporated and the residue was partitioned between 100 mL 5% Na_2CO_3 and 100 mL EtOAc. The aq layer was collected and the pH was adjusted to about 4 with 4M HCl. The aq layer was extracted with a 2:1 ethyl acetate/THF mixture. The combined organic layers were dried over $MgSO_4$ and evaporated to leave 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetic acid as a white solid, 0.5 g.

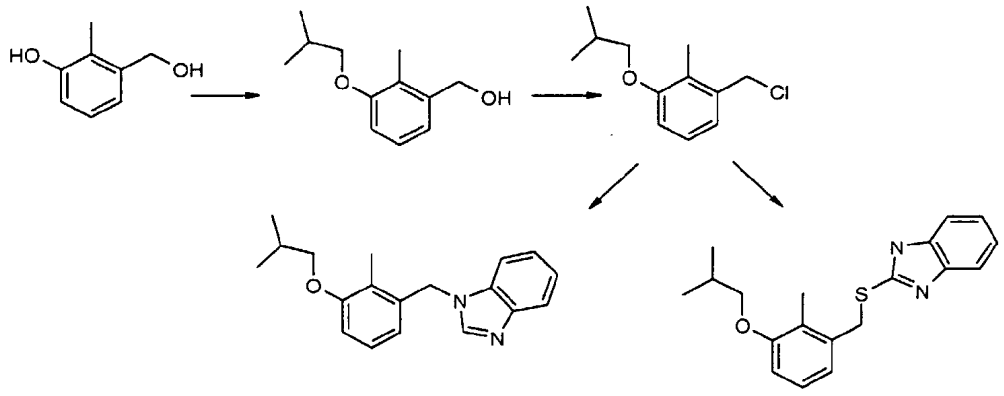
2-{3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}-1-(4-morpholinyl)-1-ethanone

100 mg of 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}acetic acid was dissolved in 2 mL of DMF, 30 mg morpholine and 120 mg of HBTU were added. The mixture was stirred for 18 hours, diluted with ethyl acetate, washed with 5% $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to give 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}-1-(4-morpholinyl)-1-ethanone, 110 mg.

2-({2-Methyl-3-[2-(4-morpholinyl)ethoxy]benzyl}sulfanyl)-1*H*-benzimidazole

2-{3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenoxy}-1-(4-morpholinyl)-1-ethanone, 0.7 g, was dissolve in 20 mL THF. 0.2 g lithium aluminum hydride was added, and the mixtue was warmed to 70 °C for 45 minutes. Na_2SO_4-$10H_2O$ was added, the mixture was filtered, concentrated and purified by column chromatography (SiO_2 , ethyl acetate) to give 2-({2-methyl-3-[2-(4-morpholinyl)ethoxy]benzyl}sulfanyl)-1*H*-benzimidazole as a white foam, 0.42 g.

Scheme 6



(3-Isobutoxy-2-methylphenyl)methanol

2-Methyl-3-hydroxymethylphenol [prepared by lithium aluminum hydride reduction of 2-methyl-3-hydroxybenzoic acid], 1 g, isobutyl bromide, 1.6 mL, and K_2CO_3, 3 g, were combined in 10 mL DMF and stirred at 70 °C for 1 day. The mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and evaporated to give (3-isobutoxy-2-methylphenyl)methanol as a yellow waxy solid, 1.15 g.

1-(3-Isobutoxy-2-methylbenzyl)-1*H*-benzimidazole

0.5 g (3-isobutoxy-2-methylphenyl)methanol was dissolved in 3 mL CH_2Cl_2, and 0.7 mL $SOCl_2$ was carefully added. The mixture was stirred for 30 min., then concentrated to give crude 1-(chloromethyl)-3-isobutoxy-2-methylbenzene. The crude chloride sample was dissolved in 3 mL DMF, and 0.26 g benzimidazole and 0.6 g K_2CO_3 were added. The

suspension was stirred at rt overnight. The mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and evaporated to give a residue which was purified by flash chromatography, silica gel, 20-50% ethyl acetate/Hexane. 1-(3-isobutoxy-2-methylbenzyl)-1*H*-benzimidazole was thus obtained as an off-white solid, 0.6g. Mass spec.; M+H=295.

2-[(3-Isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole

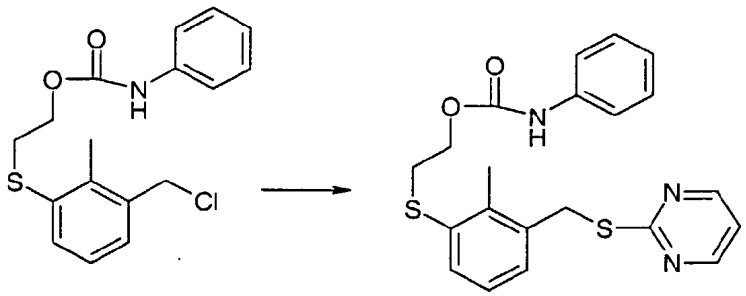
2-Mercaptobenzimidazole, 2 g, was dissolved in a solution of 10 mL water, 30 mL methanol, and 0.53 g NaOH, and cooled on an ice bath. A solution of 3.2 g 1-(chloromethyl)-3-isobutoxy-2-methylbenzene in 50 mL methanol was added and the reaction was stirred at room temp. for 6 hours. The solvents were evaporated and the residue was partitioned between 600 mL CH_2Cl_2 and 300 mL of 5% Na_2CO_3, the org. layer was collected, dried over Na_2SO_4 and evaporated to give 3.1 g 2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole as a light yellow solid.

Compound 105 can be made by a similar scheme by using 2-mercaptoindole in place of 2-mercaptobenzimidazole.

Compound 110 can be made by a similar scheme by using 2-mercaptobenzothiazole in place of 2-mercaptobenzimidazole.

Compound 111 can be made by a similar scheme by using 2-mercaptobenzoxazole in place of 2-mercaptobenzimidazole.

Scheme 7

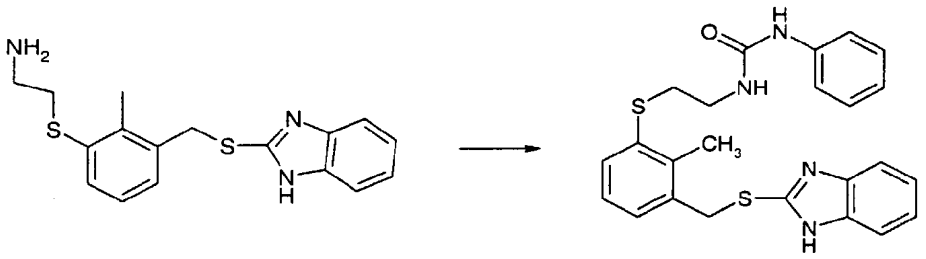


2-({2-Methyl-3-[(2-pyrimidinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate

To a solution of 135 mg of 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}ethyl phenylcarbamate in 2 mL DMF was added 65 mg of 2-thiopyrimidine, and 600 mg K_2CO_3. The suspension was stirred vigorously at RT for 1.5 hrs. The mixture was diluted to 25 mL with ethyl acetate, washed with 15 mL water, 2 X 15mL 1N KOH, 15mL brine, and dried over $MgSO_4$. Evaporation gave a thick oil. Purification by flash chromatography, silica gel, 10-

30% ethyl acetate/hexane gave 2-({2-methyl-3-[(2-pyrimidinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate as a waxy solid, 130 mg. Mass spec.; M+H=412.

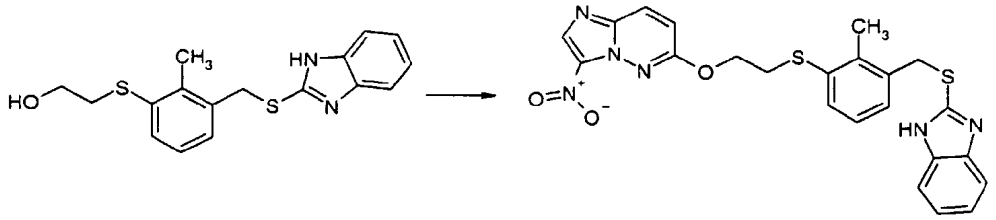
Scheme 8



N-[2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-phenylurea

100 mg of the 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanamine was dissolved in 2 mL of DMF and 36 mg of phenyl isocyanate was added. The mixture was stirred at rt overnight. The reaction was evaporated, and the crude compound was purified by reverse phase preparative HPLC to give *N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-phenylurea as a white powder, 85 mg. Mass spec.; M+H=449.

Scheme 9

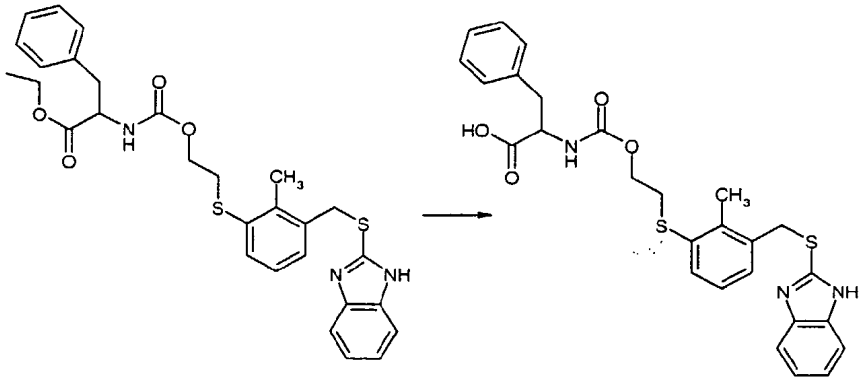


6-[2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]-3-nitroimidazo[1,2-*b*]pyridazine

To a solution of 330 mg of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol in 30 mL DMF was added 160 mg sodium hydride (60% dispersion in oil), the suspension was stirred for 30 min, then 199 mg of 6-chloro-3-nitroimidazo[1,2-*b*]pyridazine (Kobe, J.; Stanovnik, B.; Tisler, Miha. *Tetrahedron* (1968), 24(1), 239) was added. After stirring the suspension overnight at rt, 5 mL water was added carefully, then the mixture was concentrated under vacuum to leave a brown solid residue. The residue was stirred with acetone and filtered, the filtrate was concentrated and the resulting solids were rinsed with hot ethanol to yield 6-[2-({3-[(1*H*-benzimidazol-2-

ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]-3-nitroimidazo[1,2-*b*]pyridazine as a light brown powder, 140 mg.

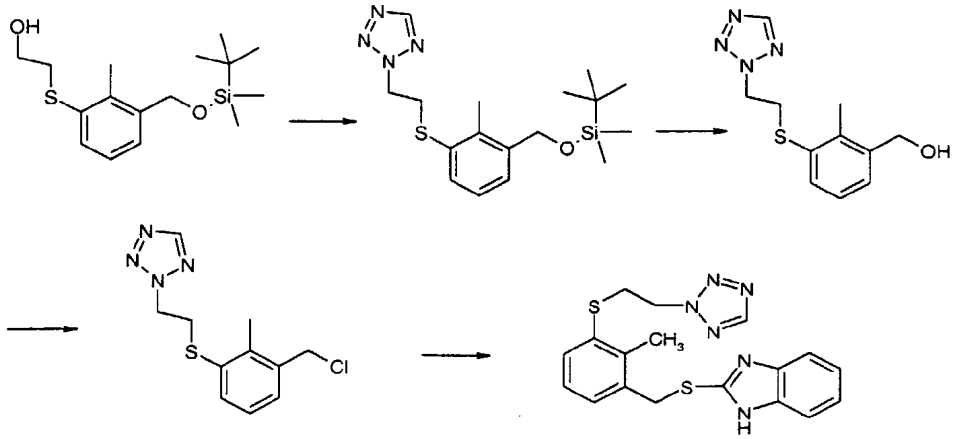
Scheme 10



***N*-{[2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}phenylalanine**

25 mg of ethyl 2-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}-sulfanyl)ethoxy]carbonyl}amino)-3-phenylpropanoate was combined with 0.1 mL 1M KOH, and 0.5 mL dioxane to give a clear solution. After stirring for 1hr at rt the reaction was diluted with water, extracted twice with ethyl acetate, the aq layer was acidified with conc HCl and extracted three times with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to yield a clear oil. Trituration with 1:1 ether/hexane gave *N*-{[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}phenylalanine as a white solid: 20 mg. Mass spec.; M+H=522.

Scheme 11



2-(2-{[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole

2-{[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}-1-ethanol, 1.2 g, triphenylphosphine, 1.6 g, and tetrazole, 0.42 g, were combined in 10 mL THF to give a clear solution. The mixture was cooled to 0 °C, and 0.94 mL diethylazodicarboxylate was added. The reaction was allowed to slowly come to rt while stirring overnight. Evaporation and purification by flash chromatography, silica gel, 9:1 hexane : ethyl acetate, gave 2-(2-{[3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole as an oil, 770 mg.

(2-Methyl-3-{[2-(2*H*-1,2,3,4-tetraazol-2-yl)ethyl]sulfanyl}phenyl)methanol

2-(2-{[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole, 770 mg, was dissolved in 20 mL THF and treated with 3 mL 75% aq. TBAF (tetrabutylammonium fluoride). The solution was stirred at rt overnight, concentrated, diluted with ethyl acetate, washed with 10% citric acid, then brine and dried over Na_2SO_4. Evaporation and purification by flash chromatography, silica gel, 1:1 hexane : ethyl acetate, gave (2-methyl-3-{[2-(2*H*-1,2,3,4-tetraazol-2-yl)ethyl]sulfanyl}phenyl)methanol, 500 mg.

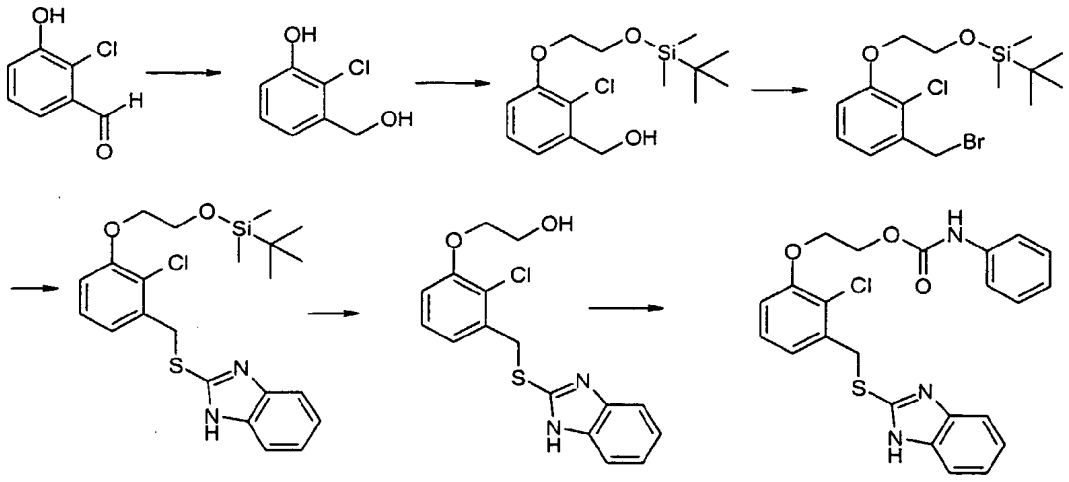
2-(2-{[3-(Chloromethyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole

To a solution of 100 mg of (2-methyl-3-{[2-(2*H*-1,2,3,4-tetraazol-2-yl)ethyl]sulfanyl}phenyl)methanol in 4 mL methylene chloride at 0 °C was added 1 mL thionyl chloride. The cold bath was removed and the mixture was stirred at rt for 1.5 hrs. Evaporation to dryness gave 2-(2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole, 105 mg.

1*H*-Benzimidazol-2-yl 2-methyl-3-{[2-(2*H*-1,2,3,4-tetraazol-2-yl)ethyl]sulfanyl}benzyl sulfide

2-(2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}ethyl)-2*H*-1,2,3,4-tetraazole, 105 mg, was dissolved in 2 mL DMF, 1 g K_2CO_3 and 100 mg 2-thiobenzimidazole were added and the suspension was stirred at rt overnight. The mixture was diluted with water, extracted with methylene chloride, washed with brine, dried over $MgSO_4$, and evaporated. Purification by flash chromatography, silica gel, 1.5 : 1 ethyl acetate : hexane gave 1*H*-benzimidazol-2-yl 2-methyl-3-{[2-(2*H*-1,2,3,4-tetraazol-2-yl)ethyl]sulfanyl}benzyl sulfide as an off-white solid, 70 mg. Mass spec.; M+H=383.

Scheme 12



2-Chloro-3-(hydroxymethyl)phenol

2 g 2-chloro-3-hydroxybenzaldehyde (Ginsburg, D. *J.Amer.Chem.Soc.* 1951(73), 702) was dissolved in 30 mL THF / 10 mL methanol / 20 mL 1N KOH. 1 g $NaBH_4$ was added. After stirring at RT for 1.5 hrs, the mixture was diluted with water and extracted with ether (2X). The aqueous layer was acidified with conc. HCl, and extracted with ethyl acetate (2X). The pooled ethyl acetate layer was dried over $MgSO_4$ and evaporated to give 2-chloro-3-(hydroxymethyl)phenol as a white solid, 2.02 g.

[3-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorophenyl]methanol

2-Chloro-3-(hydroxymethyl)phenol, 0.317 g, K_2CO_3, 0.264 g, and (2-bromoethoxy)(*tert*-butyl)dimethylsilane, 0.429 mL, were combined in 10 mL acetonitrile. The suspension was refluxed for 18 hrs, and an additional 0.2 mL (2-bromoethoxy)(*tert*-butyl)dimethylsilane was added. After refluxing the mixture an additional 24 hrs, it was filtered, and evaporated to give a crude residue. Purification by column chromatography (8:2 hexane : ethyl acetate) gave [3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorophenyl]methanol as a clear oil, 0.42 g.

{2-[3-(Bromomethyl)-2-chlorophenoxy]ethoxy}(*tert*-butyl)dimethylsilane

N-bromosuccinimide, 0.47 g, was dissolved in 20 mL methylene chloride and cooled to 0 °C. Dimethylsulfide, 0.213 mL, was added slowly and the mixture was stirred for 30 minutes at 0 °C. A solution of 0.42 g [3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorophenyl]methanol in 5 mL methylene chloride was added, and the reaction was allowed to proceed at RT for 2 h. The mixture was concentrated to give crude {2-[3-(bromomethyl)-2-

chlorophenoxy]ethoxy}(*tert*-butyl)dimethylsilane, 0.56 g, used in the next step without any further purification.

2-{[3-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorobenzyl]sulfanyl}-1*H*-benzimidazole

0.5 g {2-[3-(bromomethyl)-2-chlorophenoxy]ethoxy}(*tert*-butyl)dimethylsilane was combined with 0.2 g benzimidazole and 4 mL 1 M NaOH in 12 mL ethanol. The solution was stirred for 2.5 hrs, and the ethanol was evaporated to yield a slurry. Dilution with ethyl acetate, extraction with water, then sat. NaCl gave a clear solution. The solution was dried over $MgSO_4$, and evaporated to give 2-{[3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorobenzyl]sulfanyl}-1*H*-benzimidazole as a white foam, 0.53 g.

2-{3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}-1-ethanol

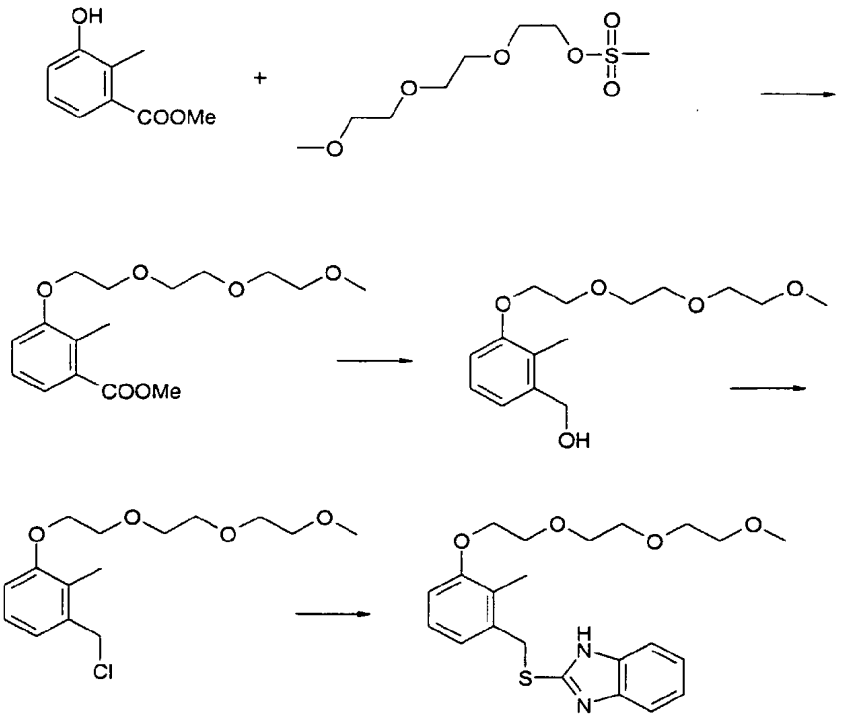
0.53 g 2-{[3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-chlorobenzyl]sulfanyl}-1*H*-benzimidazole was dissolved in 10 mL THF and 0.52 mL 2.73 M aqueous tetrabutylammonium fluoride was added. The solution was stirred for 2 hrs, diluted with water, and extracted with ethyl acetate. The organic phase was washed with sat. NaCl, dried over $MgSO_4$ and evaporated to yield 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}-1-ethanol as 0.4 g white foamy oil.

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}ethyl phenylcarbamate

0.4 g 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}-1-ethanol was dissolved in 5 mL chloroform and 0.15 mL phenyl isocyante was added. The mixture was stirred at RT for 2 hrs, diluted with chloroform, washed with water, and sat. NaCl. The solution was dried over $MgSO_4$ and evaporated to yield 2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}ethyl phenylcarbamate as 0.52g white solid.

Compounds 119 and 120 can be made by a similar route, but using 2-methoxy-3-(hydroxymethyl)phenol (see Chemistry Letters, 1986,871) in place of 2-chloro-3-(hydroxymethyl)phenol.

Scheme 13



Methyl 2-methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzoate

Methyl 2-methyl-3-hydroxybenzoate [Fringuelli, F.; Mancini, V.; Taticchi, A. *Tetrahedron*, **1969**, *25*, 4249] (0.5 g) was dissolved in 10 mL MeCN, anhydrous K_2CO_3 (1 g) was added followed by 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate [prepared by reaction of the corresponding alcohol with methanesulfonyl chloride] (1.09 g). The mixture was allowed to react at reflux over night, cooled, filtered, and taken to dryness. The residue was dissolved in CH_2Cl_2 and washed with diluted NaOH (aq) and brine. The organic layer was collected, dried, and evaporated furnishing 0.56g of the title compound which was used without further purification.

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl alcohol

A solution of Methyl 2-methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzoate (2.1 mmol) in THF (10 mL) was gently added to a stirred suspension of $LiAlH_4$ (4.5 mmol) in 20 mL THF, then heated to reflux for 2 hours. The reaction was quenched with 0.25 mL water, 0.5 mL 2M NaOH, and 0.25 mL water. The mixture was refluxed for another hour and then filtered to remove the solids. The filtrate was evaporated affording 0.28 g of the title compound.

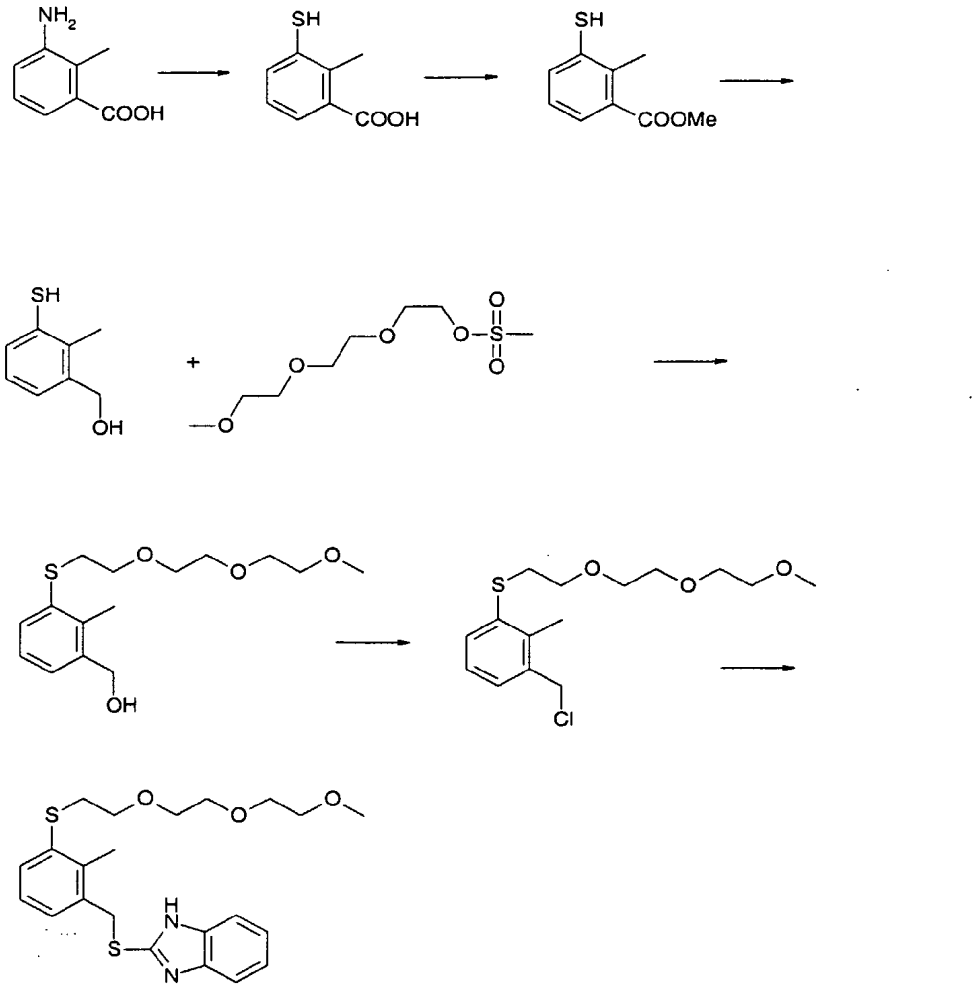
2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl chloride

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl alcohol (1.1 mmol) was dissolved 5 mL CH_2Cl_2 and treated with 0.2 mL $SOCl_2$ for 30 min at ambient temperature. The solvent and excess reagent were evaporated leaving a quantitative yield of the title compound which was used immediately in the next step.

2-[(3-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole

2-mercaptobenzimidazole (0.18 g, 1.18 mmol), suspended in 3 mL MeOH, was treated with 2 M NaOH (1.3 mL, 2.6 mmol) and allowed to form a solution. 2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl chloride (0.33 g, 1.08 mmol) was added and reacted for 18 h at ambient temperature. The solvents were evaporated and the residue partitioned between water and CH_2Cl_2 (4 x 25 mL). The organic layers were combined, dried, and evaporated. Reverse phase preparative LC afforded 115 mg (26%) of the title compound. Compound 107 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate.

Scheme 14



2-Methyl-3-mercapto-benzoic acid

3-Amino-2-methylbenzoic acid, 11.3 g, was dissolved in H_2O (100 mL) and conc. HCL (15 mL) was added at 0 °C. $NaNO_2$ (5.5g) in H_2O (40 mL) was added to the above suspension over 30min. The above diazonium salt was kept at 0 °C and added slowly (over 40 min) to a solution of potassium ethylxanthogenate (14 g) while the pH continually was adjusted to 8 with Na_2CO_3. The mixture was stirred for 30 minutes, cooled to ambient temperature, and poured onto a mixture of 300 mL concentrated HCl and 700 mL of ice water. The precipitate was collected, taken up in water (300 mL), and treated with NaOH (6 g) at reflux for 20 h. The mixture was poured onto a mixture of 40 mL concentrated HCl in 300 mL ice water and extracted with 3 × 500 mL CH_2Cl_2. The combined organic layers were dried and evaporated furnishing 7 g of the title compound as yellow crystals (which slowly oxidized to the corresponding disulfide upon standing)

2-Methyl-3-mercapto-methylbenzoate

2-Methyl-3-mercapto-benzoic acid (14.7 g) was dissolved in 250 mL of MeOH and a few drops of conc. H_2SO_4 was added. The mixture was heated to reflux for 48 hours and then allowed to cool to ambient temperature before the bulk MeOH was evaporated. The residue was dissolved in Et_2O and washed with 4 x 50 mL H_2O and 50 mL brine. The organic layer was collected, dried, and evaporated leaving 14.8 g of the title compound as a viscous yellow oil (which slowly oxidized to the corresponding disulfide upon standing.

2-Methyl-3-mercapto-benzylalcohol

A solution of 2-Methyl-3-mercapto-methylbenzoate (2.0 g) in THF (5 mL) was added drop wise to a suspension of $LiAlH_4$ (1.32 g) in THF (100 mL) under dry and inert conditions. The mixture was heated to reflux for 2 h and then quenched with 2 mL of water, 4 mL of 2 M NaOH, and another 2 mL of water. After refluxing for another hour, solids were filtered off and washed with THF and methanol. The combined filtrates were evaporated and the residue partitioned between 2M HCl and EtOAc. The organic layer was collected, dried, and evaporated to yield 1.9 g 2-Methyl-3-mercapto-benzylalcohol, contaminated with the corresponding disulfide as an oil. This material could be used in the next step without further purification.

2-Methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)ethylthio)benzyl alcohol

A mixture of 2-Methyl-3-mercapto-benzylalcohol and its disulfide (50 mg, 0.325 mmol monomer) in dioxane/water (4/1) (1 mL) and a small amount of concentrated HCl was reacted with PPh_3 (26 mg, 0.1 mmol) for 1 h at ambient temperature in an inert atmosphere. The solvents were removed and the residue taken up in MeCN (1 mL) and reacted with Et_3N (290 mL, 2.08 mmol) and 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate [prepared by reaction of the corresponding alcohol with methanesulfonyl chloride] (0.30 g, 1.24 mmol) for 3 days at ambient temperature. The solvent was evaporated and the residue partitioned between EtOAc and water. The organic layer was collected, dried, and taken to dryness. The product was purified on silica gel (pentane/Et_2O; 6/4 to 0/10) furnishing 50 mg of the title compound as a colorless oil.

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethylthio]benzyl chloride

2-Methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)ethylthio)benzyl alcohol (0.17 mmol) was dissolved in 2 mL CH_2Cl_2 and treated with 0.1 mL $SOCl_2$ for 30 min at ambient temperature. The solvent and excess reagent were evaporated leaving a quantitative yield of the title compound which was used immediately in the next step.

2-{[3-({2-[2-(2-Methoxyethoxy)ethoxy]ethyl}sulfanyl)-2-methylbenzyl]sulfanyl}-1*H*-benzimidazole

2-Mercaptobenzimidazole (0.33 g, 2.16 mmol), suspended in 6 mL MeOH, was treated with 2 M NaOH (2.6 mL) and allowed to form a solution. 2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethylthio]benzyl chloride (0.58 g, 1.80 mmol) was added and reacted for 18 h at ambient temperature. The solvents were evaporated and the residue partitioned between water and CH_2Cl_2 (4 x 25 mL). The organic layers were combined, dried, and evaporated. Reverse phase preparative LC afforded 0.47 g of the title compound.

Compound 109 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate.

Compound 112 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with isobutyl bromide.

Compound 115 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate, and 2-mercaptobenzimidazole replaced with 5-carboethoxy-2-mercaptobenzimidazole.

Compound 116 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate, and 2-mercaptobenzimidazole replaced with 5-(propan-1-one)-2-mercaptobenzimidazole.

Compound 117 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate, and 2-mercaptobenzimidazole replaced with 5-amino-2-mercaptobenzimidazole.

Compound 118 can be prepared by a similar scheme by replacing 2-[2-(2-methoxyethoxy)ethoxy]ethyl methanesulfonate with 3,6,9,12,15-pentaoxahexadec-1-yl methanesulfonate, and 2-mercaptobenzimidazole replaced with 5-(hydroxymethyl)-2-mercaptobenzimidazole.

Table 1 shows which compounds can be made by each of Schemes 1 to 14 or by schemes that are similar to schemes 1 to 14, but differ in one or more reagents as will be readily apparent to the skilled person taking into account the final compound.

Table 1

SCHEME	COMPOUND NO.
1	1-37
2	38-54
3	55-82
4	83, 84, 113, 114
5	104
6	103, 105, 110, 111
7	85-96
8	97, 98
9	99
10	100
11	101, 102
12	119-122
13	106, 107
14	108, 109, 112, 115-118

ASSAYS

Microdilution assay

The microdilution assay tests the anti-*H. pylori* activity of compounds. In this assay, MICs (Minimum Inhibitory Concentrations) were determined against four *H. pylori* strains, including ATCC 43504, that exhibit different susceptibilities to known antibiotics. The tests were performed in 24-well microtiter plates in which the medium, the inoculum, and the antibiotic solutions were distributed in the wells. Serial dilutions were prepared in 24-well plates containing a total volume of 2 mL medium per well. Cultures were resuspended in Brucella broth (OD_{600} of 0.6) and 50 µl of these cultures were inoculated into each well to give a final concentration of 10^7 cells per mL (OD_{600} of less than 0.03, which is the same as that of the non-inoculated control). The plates were then incubated for two days and the amount of growth recorded (OD_{600}) with a plate reader (Molecular Devices, Sunnyvale, California). The plates were incubated in a controlled microaerophilic atmosphere (5% O_2, 10% CO_2 and 85% N_2) that assured optimal growth of the bacterial strains and high

reproducibility of results. The MIC was defined as the lowest concentration of antibiotic resulting in complete inhibition of growth.

MIC values <10μg/mL are indicative of anti-*Helicobacter pylori* activity. Compounds according to the invention were tested in this assay and give MIC values in this range.

Selectivity Assays

Standard agar dilution protocols were used to determine the effect of compounds of the invention on panels of Gram negative and Gram positive bacteria. The effects on both aerobic ["Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition; Approved Standard" NCCLS Document M7-A4 Vol. 17 No. 2, January 1997] and anaerobic ["Methods for Antimicrobial Susceptibility Testing of anaerobic Bacteria -Third Edition; Approved Standard" NCCLS Document M11-A3 Vol. 13 No. 26, December 1993] organisms were measured. Compounds of the invention had no effect in these assays at concentrations of greater than ten times the corresponding MICs determined vs. *Helicobacter pylori* in the microdilution assay.

The invention relates in one aspect to a compound of formula I for use as a medicament. The compound can be provided as part of a pharmaceutical formulation which alo includes a pharmaceutically acceptable diluent or carrier (e.g., water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (e.g., lipid emulsions), suppositories, ointments, creams, drops, suspensions (e.g., aqueous or oily suspensions) or solutions (e.g., aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsfying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol. The formulation may contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intra-muscular administration, the patient may receive a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intra-muscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is

approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 100mg and 1g of the compound of the invention.

The following illustrate representative pharmaceutical dosage forms containing the compound of the invention, or a pharmaceutically acceptable salt or solvate thereof (hereafter referred to as "compound X"), for therapeutic or prophylactic use in humans.

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/mL)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

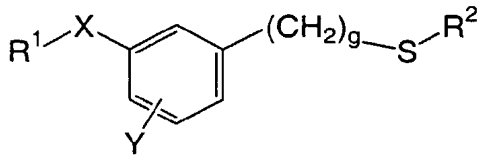
Buffers, pharmaceutically acceptable co-solvents (e.g., polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Another aspect of the invention relates to the use of a compound of formula I, in the manufacture of a medicament, for the therapeutic and/or prophylactic treatment of *Helicobacter pylori* infection in a mammalian host, e.g. a human. By "therapeutic treatment", we mean the eradication or suppression of a pre-existing *Helicobacter pylori* infection in the host.

In a further aspect of the invention, there is provided a method of therapeutically treating or preventing *Helicobacter pylori* infection in a mammal (e.g., a human), the method comprising administering (e.g., orally) to the mammal a compound of formula I or a pharmaceutical formulation as described above. By "therapeutically treating", we mean bringing about the eradication or suppression of a pre-existing *Helicobacter pylori* infection in the host.

CLAIMS:

1. A compound of formula I or a pharmaceutically acceptable salt or solvate thereof



I

wherein:

X is S; SO_2; NH; N(C_{1-6}alkyl); O or CH_2;

Y is C_{1-6}alkyl; O(C_{3-8}cycloalkyl); O(C_{1-6}alkyl); Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen; NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl, or NRR´ represents an optionally substituted C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S; H; COOR″ or COR″, R″ representing H or C_{1-6}alkyl; or CH_2OH;

R^1 is $-(CH_2)_a-R^3$; $-((CH_2)_bO)_c-R^3$; $-(CH_2)_d-R^{3'}$; $-(CH_2)_aC(=O)R^3$; $-(CH_2)_dC(=O)R^{3'}$; $-((CH_2)_e-O)_{c'}-(CH_2)_f-R^{3'}$; R^3 or $R^{3'}$;

R^2 is an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S;

R^3 is H; C_{1-6}alkyl; optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S;

$R^{3'}$ is -Z-M wherein Z represents O, S or NH and M represents H, an optionally substituted mono- or bi- cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, or an optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or -Z-M represents $-C(=O)NR^6R^7$, $-NR^6R^7$, $-OC(=O)NR^8R^9$, $-NC(=O)NR^8R^9$ or $-NC(=O)R^8$;

For R^6 and R^7, either:

(i) R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10}; optionally substituted (C_{1-8}alkyl)R, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered

heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; or -C(=O)-O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and

R^7 is H; or

(ii) the structure $-NR^6R^7$ represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S, $-NR^6R^7$ being optionally substituted;

a represents an integer 1, 2, 3, 4 or 5;

each b independently represents an integer 1, 2, 3, 4 or 5;

c represents an integer 1, 2, 3, 4 or 5;

c' represents an integer 1, 2, 3, 4 or 5;

d represents an integer 1, 2, 3, 4 or 5;

each e independently represents an integer 1, 2, 3, 4 or 5;

f represents an integer 1, 2, 3, 4 or 5; and

g represents zero or an integer 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to Claim 1, wherein:

a is 1, 2 or 3;

b is 2;

c' is 1, 2, 3, 4 or 5;

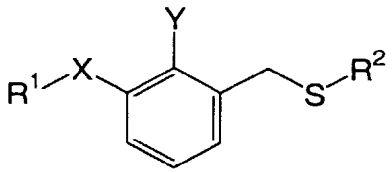
d is 1, 2 or 3;

e is 2;

f is 1, 2 or 3; and

g is 1 or 2.

3. A compound according to Claim 2, having the general structure Ib



Ib

wherein:

X is S, S(=O), $S(=O)_2$ or O;

Y is C_{1-6}alkyl, $O(C_{1-6}alkyl)$, Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal;

R^1 is $-(CH_2)_a-R^3$, $-((CH_2)_2O)_c-R^3$, $-(CH_2)_d-R^{3'}$, $-(CH_2)_aC(=O)R^3$, $-(CH_2)_dC(=O)R^{3'}$, $-((CH_2)_2O)_{c'}-(CH_2)_f-R^{3'}$;

R^3 is C_{1-6}alkyl; optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle;

$R^{3'}$ is -Z-M wherein Z represents O, S or NH and M represents H, an optionally substituted mono- or bi- cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or an optionally substituted C_{5-10} aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or -Z-M represents $-C(=O)NR^6R^7$, $-NR^6R^7$, $-OC(=O)NR^8R^9$, $-NC(=O)NR^8R^9$ or $-NC(=O)R^8$;

For R^6 and R^7, either:

(i) R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted $(C_{1-8}alkyl)$aryl wherein the aryl is C_{6-10}; optionally substituted $(C_{1-8}alkyl)R$, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; or -C(=O)-O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and

R^7 is H; or

(ii) the structure $-NR^6R^7$ represents a C_{3-8} heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S per cycle; $-NR^6R^7$ being optionally substituted;

or a pharmaceutically acceptable salt or solvate thereof.

4. A compound according to Claim 3, wherein:

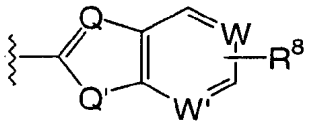
X is S or O;

R^1 is $-(CH_2)_2R^3$, $-(CH_2)_2R^{3'}$, $-CH_2C(=O)R^3$ or $-CH_2C(=O)R^{3'}$; and

R^3 is optionally substituted C_{3-8}cycloalkyl optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; optionally substituted C_{5-10}aromatic ring structure optionally containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N and S.

5. A compound according to either Claim 1, 2 or 3, wherein R^1 is selected from *-iso*-Bu, $-(CH_2CH_2O)_3CH_3$, $-(CH_2CH_2)$-4-morpholinyl, $-(CH_2CH_2O)_5CH_3$, $-(CH_2CH_2)$-1-(2-methyl-5-nitro-imidazolyl), $-(CH_2CH_2)$-1-(1,2,4-triazolyl), and $-(CH_2CH_2)$-OC(=O)NH-Ph.

6. A compound according to any one of Claims 1, 2 or 3, wherein R^2 represents



wherein:

Q is CH or N;

Q´ is NH, O or S;

W is CH or N;

W´ is CH or N; and

R^8 is C_{1-6}alkyl; O(C_{3-8}cycloalkyl); O(C_{1-6}alkyl); Hal; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen; NRR´, wherein R and R´ independently represent H or C_{1-8}alkyl, or NRR´ represents an optionally substituted C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently

selected from O, N and S, wherein the heterocyclic ring contains at least one carbon atom and contains no more than one O and no more than one S; H; $COOR^9$ or COR^9, R^9 representing H or C_{1-6}alkyl; or CH_2OH.

7. A compound of Claim 1, wherein R^1 is $-(CH_2)_a-CH_3$ or $-((CH_2)_bO)_c-CH_3$.

8. A compound according to Claim 2, wherein $R^{3'}$ is selected from -4-morpholinyl, -1-(2-methyl-5-nitro-imidazolyl), -1-(1,2,4-triazolyl) and -OC(=O)NH-Ph.

9. A compound according to any one of Claims 1 through 8, wherein g is 1.

10. A compound of Claim 1, wherein the compound is selected from:
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl isopropylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-phenoxyphenylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl pentylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,5-dimethylphenylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl (1*S*,2*R*)-2-phenylcyclopropylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl cyclohexylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-(methylsulfanyl)phenylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenethylcarbamate;
2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-(2-thienyl)ethylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl methylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-methylphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-methoxyphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-fluorophenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl benzylcarbamate;

methyl 3-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}amino)benzoate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-dichlorobenzylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-difluorophenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenyl dicarbonimidoate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-bromophenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-methylbenzylcarbamate;

ethyl 2-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}amino)-3-phenylpropanoate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,5-dimethyl-4-isoxazolylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-acetylphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl benzoylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-chloro-2-methylphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-methoxybenzylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-dichlorophenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-(dimethylamino)phenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,5-dichlorophenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,5-dimethoxyphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2,4-dimethoxyphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl (1*R*)-1-phenylethylcarbamate;

ethyl 4-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}amino)benzoate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 2-ethylphenylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-fluorobenzoylcarbamate;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]benzamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]cyclohexanecarboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-[(4*S*)-2,5-dioxoimidazolidinyl]acetamide;

tert-butyl 4-({[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]amino}carbonyl)-1-piperidinecarboxylate;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-pyrazinecarboxamide;

2-(1-adamantyl)-*N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]acetamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)acetamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-furamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-5-nitro-2-furamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-thiophenecarboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-1-benzofuran-2-carboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]nicotinamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-4-quinolinecarboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-3,5-dimethyl-4-isoxazolecarboxamide;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-5-isoxazolecarboxamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclopropylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(1,3-benzodioxol-5-ylmethy)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(1-piperidinyl)-1-ethanone;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2-furylmethyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclohexylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(tetrahydro-2-furanylmethyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-cyclopentylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2-thienylmethyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(4-morpholinyl)ethyl]acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-benzylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2,5-dimethoxyphenethyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(2-pyridinyl)ethyl]acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-[2-(1-methyl-2-pyrrolidinyl)ethyl]acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(3,3-diphenylpropyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-phenethylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-methoxyphenethyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-hexylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-isobutylacetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-pyridinylmethyl)acetamide;

N'-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetyl]-2-furohydrazide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-octahydro-1(2*H*)-quinolinyl-1-ethanone;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(benzyloxy)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-[4-(2-methoxyphenyl)-1-piperazinyl]-1-ethanone;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-[6,7-dimethoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-1-ethanone;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(4-butylphenyl)acetamide;

2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(4-methyl-1-piperazinyl)-1-ethanone;

2-[(2-methyl-3-{[2-(4-morpholinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole;

2-[(2-methyl-3-{[2-(4-methyl-1-piperazinyl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole;

2-({3-[(1*H*-imidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate;

2-[(2-methyl-3-{[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate;

2-({2-methyl-3-[(2-pyrimidinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate;

2-[(2-methyl-3-{[(1-phenyl-1*H*-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate;

2-[(3-{[(4,5-diphenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-2-methylphenyl)sulfanyl]ethyl phenylcarbamate;

2-({3-[(3*H*-imidazo[4,5-*c*]pyridin-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate;

2-({3-[(1,3-benzoxazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl phenylcarbamate;

2-({2-methyl-3-[(2-pyridinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate;

2-({2-methyl-3-[(4-pyridinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate;

2-[(2-methyl-3-{[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]methyl}phenyl)sulfanyl]ethyl phenylcarbamate;

2-({2-methyl-3-[(1,3-thiazol-2-ylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate;

2-[(3-{[(5-methoxy-1*H*-benzimidazol-2-yl)sulfanyl]methyl}-2-methylphenyl)sulfanyl]ethyl phenylcarbamate;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-phenylurea;

N-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N'*-(2-pyrazinyl)urea;

6-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]-3-nitroimidazo[1,2-*b*]pyridazine;

2-[(2-methyl-3-{[2-(2*H*-1,2,3,4-tetrazol-2-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole;

2-[(2-methyl-3-{[2-(2*H*-1,2,3,4-tetrazol-2-yl)ethyl]sulfanyl}benzyl)sulfanyl]-3*H*-imidazo[4,5-*c*]pyridine;

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole;

2-({2-methyl-3-[2-(4-morpholinyl)ethoxy]benzyl}sulfanyl)-1*H*-benzimidazole;

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1*H*-indole;

2-[(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-2-methylbenzyl)sulfanyl]-1*H*-benzimidazole;

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-yloxy)benzyl]sulfanyl}-1*H*-benzimidazole;

2-{[3-({2-[2-(2-methoxyethoxy)ethoxy]ethyl}sulfanyl)-2-methylbenzyl]sulfanyl}-1*H*-benzimidazole;

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazole;

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1,3-benzothiazole;

2-[(3-isobutoxy-2-methylbenzyl)sulfanyl]-1,3-benzoxazole;

2-{[3-(isobutylsulfanyl)-2-methylbenzyl]sulfanyl}-1*H*-benzimidazole;

2-[(2-methyl-3-{[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole;

2-[(2-methyl-3-{[2-(1*H*-1,2,4-triazol-1-yl)ethyl]sulfanyl}benzyl)sulfanyl]-1*H*-benzimidazole;

ethyl 2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazole-5-carboxylate;

1-(2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-yl)-1-propanone;

2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-amine;

(2-{[2-methyl-3-(3,6,9,12,15-pentaoxahexadec-1-ylsulfanyl)benzyl]sulfanyl}-1*H*-benzimidazol-5-yl)methanol;

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methoxyphenoxy}-1-ethanol;

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methoxyphenoxy}ethyl phenylcarbamate;

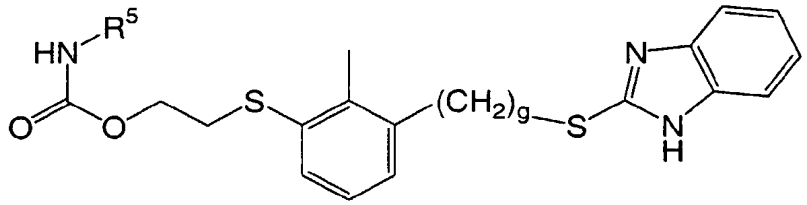
2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}-1-ethanol; and

2-{3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-chlorophenoxy}ethyl phenylcarbamate;

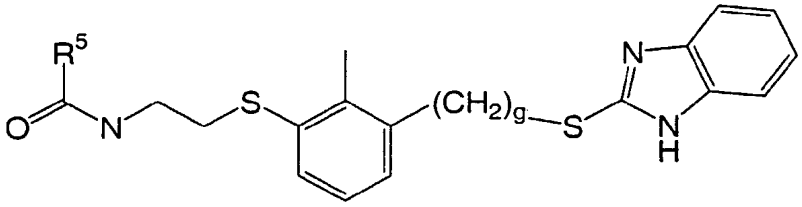
N-{[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethoxy]carbonyl}phenylalanine;

or a pharmaceutically acceptable salt or solvate thereof.

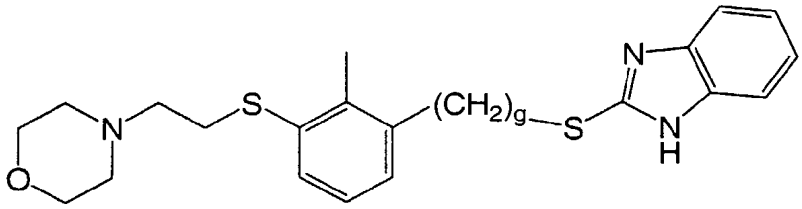
11. A compound according to Claim 1, wherein the compound is selected from compounds II, III, IV and V



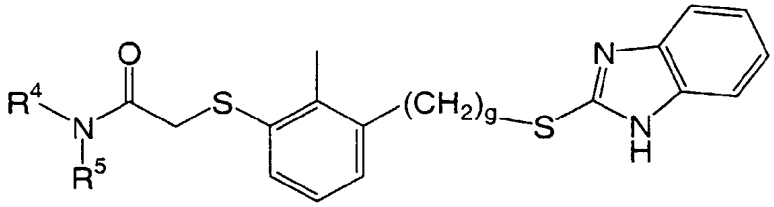
II



III



IV



V

wherein,

For R^4 and R^5, either:

(i) R^4 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; Z^2-(C_{1-8}alkyl)aryl, wherein Z^2 represents O or a bond, and the aryl is C_{6-10}, optionally substituted and optionally fused to a C_{5-10} heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted C_{6-10}aryl; an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S; (C_{1-8}alkyl)-R, wherein R represents an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring

structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted -C(=O)O(C_{1-8}alkyl); optionally substituted -C(=O)O-phenyl; optionally substituted -C(=O)(C_{1-8}alkyl); optionally substituted -C(=O)-phenyl; or -NHC(=O)R^6; and

R^5 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10} and optionally substituted; optionally substituted C_{6-10}aryl; or an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or

(ii) the structure -NR^4R^5 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S and optionally fused to a C_{6-10}ring structure, -NR^4R^5 being optionally substituted.

12. A compound according to any one of Claims 1 through 11 for use as a medicament.

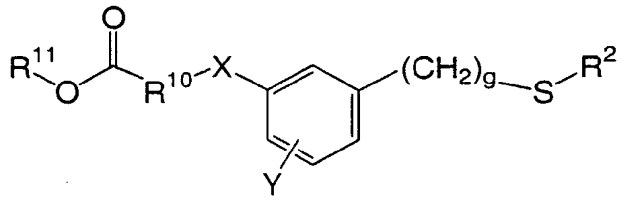
13. A pharmaceutical formulation comprising a compound according to any one of Claims 1 through 11 and a pharmaceutically acceptable diluent or carrier.

14. Use of a compound according to any one of Claims 1 through 11, in the manufacture of a medicament, for the therapeutic and/or prophylactic treatment of *Helicobacter pylori* infection in a mammalian host.

15. A method of therapeutically treating and/or preventing *Helicobacter pylori* infection in a mammal, comprising administering to the mammal a compound according to any one of Claims 1 to 11.

16. A process for preparing a compound according to Claim 1, wherein the process comprises the steps of:

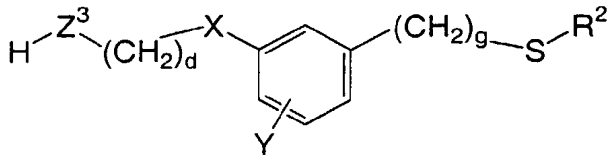
(a) reducing compound VI



VI

wherein R^{10} represents $(CH_2)_d$ or $-(CH_2)_{f-1}$-O-$(CH_2)_e$- and R^{11} represents H or C_{1-6}alkyl; or

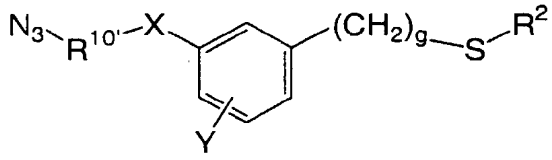
(b) reacting compound VII with R^6-NCO



VII

wherein Z^3 represents O or NH; or

(c) reducing comound VIII

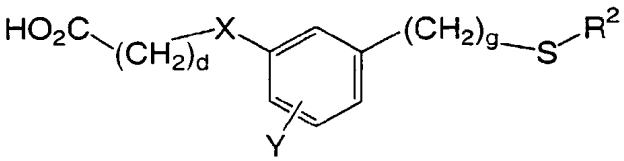


VIII

wherein $R^{10'}$ represents a bond, $(CH_2)_d$ or $-(CH_2)_f$-O-$(CH_2)_e$-; or

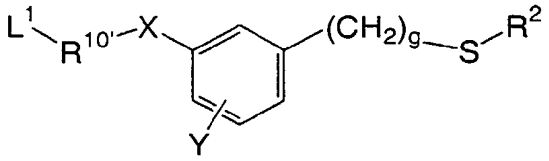
(d) reacting compound VII with R^6-COOH; or

(e) reacting compound IX with NHR^4R^5; or



IX

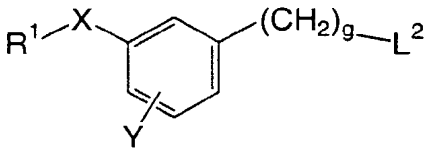
(f) reacting compound X with NHR^4R^5



X

wherein L^1 represents a leaving group and $R^{10'}$ represents $(CH_2)_d$ or $-(CH_2)_f$-O-$(CH_2)_e$-; or

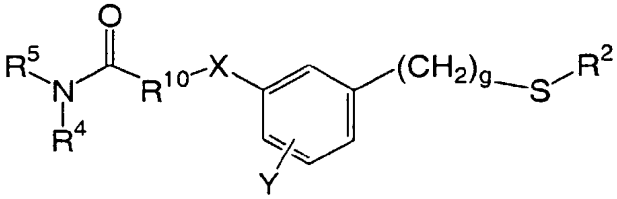
(g) reacting compound XI with R^2-SH



XI

wherein L^2 represents a leaving group; or

(h) reducing compound XII



XII

wherein,

For R^4 and R^5, either:

(i) R^4 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; Z^2-(C_{1-8}alkyl)aryl, wherein Z^2 represents O or a bond, and the aryl is C_{6-10}, optionally substituted and optionally fused to a C_{5-10} heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted C_{6-10}aryl; an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S; (C_{1-8}alkyl)-R, wherein R represents an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; optionally substituted -C(=O)O(C_{1-8}alkyl); optionally substituted -C(=O)O-phenyl; optionally substituted -C(=O)(C_{1-8}alkyl); optionally substituted -C(=O)-phenyl; or -NHC(=O)R^6; and

R^5 is H; C_{1-8}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10} and optionally substituted; optionally substituted C_{6-10}aryl; or an optionally substituted 5-, 6-, 7-, 8-, 9- or 10-membered heterocyclic ring structure containing 1, 2 or 3 heteroatoms independently selected from O, N and S; or

(ii) the structure -NR^4R^5 represents a C_{3-8}heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S and optionally fused to a C_{6-10}ring structure, -NR^4R^5 being optionally substituted;

R^6 is H; C_{1-12}alkyl; optionally substituted C_{3-8}cycloalkyl optionally fused to a benzo ring; optionally substituted (C_{1-8}alkyl)aryl wherein the aryl is C_{6-10}; optionally substituted (C_{1-8}alkyl)R, where R represents a mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S or R represents a mono-, bi- or tri-cyclic C_{3-13}cycloalkyl; optionally substituted C_{6-10}aryl; an optionally substituted mono- or bi-cyclic 5-, 6-, 7-, 8-, 9- or 10-membered heterocycle containing 1, 2, 3, 4, 5 or 6 heteroatoms independently selected from O, N and S; or -C(=O)-O-Ar, wherein Ar represents optionally substituted C_{6-10}aryl; and

R^{10} is $(CH_2)_d$ or $-(CH_2)_{f-1}$-O-$(CH_2)_e$-.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02192

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 235/28, A61K 31/4184, A61P 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0251536 A1 (FISONS PLC), 7 January 1988 (07.01.88) --	1-16
X	EP 0204215 B1 (G.D. SEARLE & CO.), 10 December 1986 (10.12.86) --	1-16
A	US 5576341 A (MITSUO MASAKI ET AL), 19 November 1996 (19.11.96) --	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2001	14-03-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02192

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☒ Claims Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box I.1

Claim 15 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

Box I.2

Present claims 1-2 relate to an extremely large number of possible compounds. In fact, the claim contains so many variables that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of the claims impossible.
Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely mainly the compounds claimed in claim 10.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0251536 A1	07/01/88	AU 7465487 A	07/01/88
		DK 319387 A	25/12/87
		FI 872774 A	25/12/87
		GB 8615416 D	00/00/00
		IL 82965 D	00/00/00
		JP 63005082 A	11/01/88
		NO 872625 A	28/12/87
		NZ 220770 A	26/02/90
		PT 85153 A,B	01/07/87
		ZA 8704446 A	27/04/88
		GB 8615417 D	00/00/00
		GB 8615418 D	00/00/00
		GB 8615419 D	00/00/00
		GB 8702683 D	00/00/00
		GB 8702685 D	00/00/00
		GB 8702686 D	00/00/00
EP 0204215 B1	10/12/86	AU 5768886 A	27/11/86
		JP 7103110 B	08/11/95
		JP 61293975 A	24/12/86
		US 5869513 A	09/02/99
		ZA 8603859 A	29/07/87
US 5576341 A	19/11/96	DE 69404200 D,T	08/01/98
		EP 0621035 A,B	26/10/94
		ES 2104223 T	01/10/97
		JP 6298611 A	25/10/94
		JP 8099808 A	16/04/96

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(19) World Intellectual Property Organization
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PCT

(10) International Publication Number
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(25) Filing Language: English

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(30) Priority Data:
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(72) Inventors; and

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(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/03707 A1

(54) Title: HEARTBURN TREATMENT

(57) Abstract: The present invention is directed to the use of an alkali metal salt of a bicarbonate, preferably sodium bicarbonate, and an effective amount of a proton pump inhibitor in combination for the treatment of heartburn symptoms.

HEARTBURN TREATMENT

FIELD OF THE INVENTION

This invention discloses use of an omeprazole-bicarbonate combination for the treatment of heartburn, and acid indigestion.

BACKGROUND OF THE INVENTION

US patent, 5,840,737, Phillips, J. issued Nov 24 1998, describes a combination of a bicarbonate salt and omeprazole. The claims are directed to treatment of gastric acid disorders (unspecified) with a single dose of a pharmaceutical composition of omeprazole or lansoprazole together with a bicarbonate salt (Na or K preferred). The dose is orally administered as an aqueous solution or suspension.

The Philips patent focuses on the prophylactic prevention of upper GI bleeding in critically ill patients. It is particularly directed toward stress ulcer prophylaxis which has become routine therapy in intensive care units in most hospitals. An inherent advantage is the ability to infuse the solution via a nasogastric tube directly into the stomach. Data indicates that the omeprazole-bicarbonate solution/suspension combine the rapid onset of pH neutralization (due to bicarbonate) with the prolonged duration of effect of the proton pump inhibitor (PPI). There is an enhancement in time to onset of action of the PPI, omeprazole. This is postulated to reflect an effect of the bicarbonate to enhance the absorption of omeprazole. Indeed, in the presence of the bicarbonate omeprazole is observed to more rapidly become available systemically, and initial absorption of omeprazole is observed within 10-12 minutes in the combination as compared to 2-3 hours for omeprazole administered as enteric coated pellets.

However, Phillips does not suggest that the administration of a PPI plus a bicarbonate would be useful as a means to provide rapid onset, and prolonged duration of effect for relief of heartburn symptoms, nor in avoiding the reocurrence of heartburn symptoms.

Omeprazole has been formulated in many different embodiments such as in a mixture of polyethylene glycols as shown in U.S. Pat. No. 5,219,870 to Kim; U.S.

Pat No. 5,395,323 to Berglund discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient.

U.S. Pat. No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH.

The ability to provide a patient with a single dose administration of a preparation which has a rapid onset of acid neutralization would be a highly desirable dosage form for the treatment or prevention of heartburn symptoms.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating and/or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

The administration preferably consists of a single dosage without requiring further administration of a second dose of a bicarbonate salt.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to single dose administration of a pharmaceutical composition for relief of heartburn symptoms. The term "heartburn symptoms" as used herein includes heartburn related to indigestion, sour stomach, upset stomach, episodic and co-incidental heartburn with meals, and heartburn related to gastroesophageal reflux of acid stomach contents. These are generally well recognized symptoms which are typically treated with, over-the-counter (OTC) medications, such as antacids, and more recently histamine H_2 receptor antagonists at reduced dosage. The treatments considered herein are the same as those symptoms for which various regulatory agencies, such as the FDA, have approved the use of H_2 receptor antagonists without prescription.

The present invention's use in the treatment of heartburn is a treatment which is safe, effective and useful for self-limiting gastrointestinal conditions. This

treatment is in contrast to the use of a proton pump inhibitor and an alkali metal bicarbonate salt for medically diagnosable gastrointestinal diseases, such as active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. The dosage administration is basically a once only treatment, and is not necessarily used for multiple daily dosing over a period of many days, weeks or long term duration, although it is recognized that it could be used as such.

Suitable proton pump inhibitors (PPI) useful in the present invention include those antisecretory compounds belonging to the class of compounds generally referred to as substituted benzimidazoles. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Also suitable for use herein are the individual enantiomers, of omeprazole, such as the (S) isomer, or a suitable salt form, such as the calcium or magnesium salts, or a combination of both such as the (S) magnesium salt of omeprazole. Other substituted benzimidazoles suitable for use herein include, but are not limited to lansoprazole, 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole; pantoprazole, 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, and rabeprazole 2[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole.

This class of compounds (the proton pump inhibitors) inhibit gastric acid secretion and do not exhibit anti-cholinergic or histamine H_2 antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H< + > /K< + > ATPase enzyme system at the secretory surface of the gastric parietal cell.

Current use of proton pump inhibitors, particularly intravenous or oral liquid dosage forms is primarily directed towards medically diagnosable treatment of ulcers, or other medical determined mucosal bleeding of the gastrointestinal tract. Combinations of various H_2-antagonists, antacids and sucralfate are other currently used treatment options as prophylaxis for such damage.

These uses are however, not directed to the prevention or the treatment of heartburn symptoms.

Several buffered omeprazole solutions have been disclosed in publications, Andersson et al., Clinical Pharmacokinetics 24(1):71-8 (1993); Landahl et al. Clinical Pharmacokinetics 23 (6); 469-76 (1992); Andersson et al., Br. J. Clin. Pharmacol., 29(5):557-63 (1990); Regardh et al., Ther. Drug Monit. 12(2):163-72 (1990);

Andersson et al., Eur. J. Clin. Pharmacol., 39(2):195-7 (1990); and Pilbrant et al., Gastroenterol Suppl., 108:113-20 (1985).

All of the buffered omeprazole solutions described in these publications were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, the repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration.

The bicarbonate was not given for its acid neutralizing capacity as an antacid, but for its use in preventing the degradation of the PPI. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required in contrast to the present invention. In these above-cited studies, as much as 48 millimoles of sodium bicarbonate in 300 ml of water were ingested in association with a a single dose of omeprazole for oral administration.

The present invention does not require the ingestion of excessive volumes of bicarbonate with water. Furthermore, the enhancement in onset of the PPI's action allows use of a minimal dose to achieve rapid and long-lasting relief of heartburn symptoms. The use of the combination of the PPI and bicarbonate permits using the PPI at dosages which are often suboptimal for standard Rx therapeutic applications (e.g., healing of duodenal or gastric ulcers, healing esophageal erosions, etc.). In the case of omeprazole, a dosage of about 10 to about 20 mg is desired.

Another aspect of the present invention is a dosage form of the omeprazole and bicarbonate which can be utilized to quickly make an omeprazole solution/suspension which is supplied in a solid form, such as in a powder form of a sachet, or as readily dispersible tablet or capsule. Alternatively the solid dosage form of omeprazole and bicarbonate, such as in a compressed tablet or capsule for oral ingestion may also be suitable, or even desired for use by the patient for the treatment of their heartburn symptoms.

An advantage of either the solution/suspension formulation or the solid dosage formulation are that both provide a means for the rapid onset and prolonged duration of effect for relief of heartburn symptoms and avoid the recurrence of these heartburn symptoms.

The pharmaceutical composition of the present invention may be prepared in accordance with Phillips, J., US Patent No. 5,840,737 whose disclosure is incorporated

herein by reference in its entirety. The composition may also be prepared by mixing omeprazole or other substituted benzimidazoles and derivatives thereof, with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole powder or granules, which may be enteric coated or not, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. The concentration of omeprazole in the solution/suspension can range from approximately 0.25 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 0.5 mg/ml to approximately 2 mg/ml.

The pharmaceutically acceptable alkali metal salt of a bicarbonate is preferably a Group IA metal salt, such as potassium or sodium. The concentration of the bicarbonate salt in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt ranges from approximately 7.5 percent to approximately 10.0 percent. In one embodiment of the present invention, sodium bicarbonate is the preferred salt and is present in a concentration of approximately 8.4 percent. A sufficient acid neutralizing capacity (ANC) amount is necessary and that will range from about 5 to about 40 ANC values, preferably from about 18 to 40 ANC values. It should be noted that the FDA considers an ANC value of 5 to be the minimum amount useful as an antacid. In the case of sodium or potassium bicarbonate preferred range is 18 to 40mEq, for calcium bicarbonate it is from about 36 to 80 mEq.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 1-2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 2.0 meq (mmole) per 1-2 mg of omeprazole, preferably 0.5 to 1.5mEq/1-2 mg of omeprazole.

In an another aspect of the present invention, enterically-coated omeprazole granules may be used and admixed with the sodium or potassium bicarbonate ($NaHCO_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension for use in accordance with the present invention. Alternatively a solid dosage formulation of the enteric coated granules with the bicarbonate may be made and placed into capsules, or using the many techniques now known in the art, formulated into a compressed tablet.

Alternatively, micronized granules of a PPI, such as omeprazole may be used in place of conventional granules or powder. The process known as micronization is utilized in order to produce a particle having a smaller diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size

increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

The formulation may contain suitable flavoring agents for use herein including, but not limited to, wintergreen, orange, grapefruit, chocolate, and cherry-raspberry. The amount of flavouring present in the formulation may be from about 0.1% to about 5.0% by weight of the composition.

The solid formulations may optionally contain suitable disintegrants such as, but not limited to, sodium starch glycolate [Explotab®], crosslinked polyvinylpyrrolidone, corn starch, acacia , Croscarmellose of sodium [Ac-di-sol®], sodium carboxymethylcellulose, veegum, or alginates. The amount of disintegrant present may be from about 1% to about 10.0% by weight of the composition.

The formulation may also include additional diluents or fillers which are preferably swellable agents, and may include, but are not limited to, various grades of microcrystalline cellulose, such as Avicel PH101, Avicel PH102, & Avicel PH200; corn starch; or Starch 1500. The amount of diluent or filler present in the formulation may be from about 1% to about 90.0% by weight of the composition.

The dosage form may also optionally contain suitable lubricants or wetting agents, such as but not limited to, magnesium stearate, stearic acid and its pharmaceutically acceptable alkali metal salts, calcium stearate, sodium stearate, Cab-O-Sil, Syloid, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate or talc. Preferably, a suitable lubricant is magnesium stearate or stearic acid. Preferably, a suitable wetting agent is a surfactant, such as sodium lauryl sulfate. The amount of lubricant present in the formulation may be from about 0.1% to about 10.0% by weight of the composition, wherease the amount of wetting agent may be from about 0.1 – 20% by weight.

The formulation may also include additional binding agents, such as polyvinylpyrrolidone, (PVP), or Povidone 29K/32. The amount of binding agent present in the formulation may be from about 0.1% to about 30.0% by weight of the composition.

The formulation may also include coloring agents, or pigments, such as FD&C or D&C approved lakes and dyes, iron oxide and titanium dioxide. The amount of pigment present may be from about 0.1% to about 5.0% by weight of the composition.

Additional other conventional pharmaceutical diluents or excipients may also be included, as needed, in the admixture. Suitable excipients which may be employed include, for example, fillers, binders, lubricants, binders, compression aids, and wetting agents. To further assist patient compliance, the formulation may also contain sweeteners such as various natural sugars, aspartame, sodium cyclamate and sodium saccharinate; in addition to the flavorants. The amount of sweetner present may be from about 0.1% to about 20.0% by weight of the composition.

The formulations may also be manufactured in a concentrated form, such as an effervescent tablet, for oral administration upon admixture with water. Suitable effervescent formulations for use herein are well known in the art.

The following data illustrates the utility of the pharmaceutical composition of the present invention.

Comparison of onset of acid inhibition between omeprazole alone and the omeprazole – bicarbonate combination.

Khoury, *et al.* studied onset of acid inhibition following a single postprandial administration of omeprazole 10 or 20 mg in healthy volunteers. Khoury, et al., *Am. J. Gastroenterol.* ***93:*** 1619, (1998). The effect of omeprazole was compared with ranitidine, 75 and 150 mg. Gastric acid was measured via an intragastric pH probe. The design was a randomized crossover in 24 subjects. A standardized breakfast was consumed, drug was administered once intragastric pH returned to pH < 2.0, and intragastric pH recorded for 6 hr. Omeprazole, at both 10 and 20 mg failed to elevate intragastric pH to values ≥ 3.0 during the 6 hour postprandial recording period. In contrast, ranitidine 75 mg and 150 mg elevated intragastric pH > 3.0 within 178 and 145.5 min of dosing, respectively, and sustained pH > 3.0 for 2 and 3 hours of the recording period. Hence in this study, a single postprandial dose of 10 or 20 mg omeprazole had no effect on intragastric acidity for 6 hours following administration in healthy individuals.

Similarly, Decktor, *et al.* compared effects of single administrations of omeprazole 10 or 20 mg, famotidine 10 mg and placebo on meal-stimulated gastric acid secretion. Decktor, et al., *Am. J. Gastroenterol.* ***92:*** 1588, (1997). In a blinded, placebo-controlled cross-over study, each of 12 subjects randomly received the treatments one hour prior to intragastric infusion of a liquid peptone meal (600 ml 8% peptone, pH 4.0) designed to maximally stimulate acid output. Intragastric pH was maintained at pH 4.0 by continuous infusion of NaOH. Compared to placebo,

onset of significant acid antisecretory activity was observed 45 min, 75 min and 90 min following meal infusion for famotidine, omeprazole 20 mg and omeprazole 10 mg respectively. Over a 5 hr recording period. 10 mg famotidine reduced the amount of titrant required to maintain pH at 4.0 by 81%, while reductions of 56% and 27% were obtained with 20 mg and 10 mg omeprazole respectively. Famotidine 10 mg had a significantly faster onset of action and significantly greater antisecretory effect than omeprazole

The Phillips U.S. patent No. 5,840,737 in contrast, reports that single administration of bicarbonate + omeprazole elevates intragastric pH in critically ill patients from 3.0 ± 0.7 to 7.0 ± 0.6 within 2 hours after dosing. The dose was 20 mEq ANC provided by bicarbonate and a 40 mg omeprazole dose. Neutralization was then maintained by single daily administration of omeprazole (10 mEq ANC + 20 mg omeprazole) over the course of the study.

Lack of Effect of omeprazole in prevention of meal-induced heartburn

Decktor recently reported a single administration of omeprazole 10 or 20 mg failed to prevent meal-induced heartburn. Decktor, et al., *Am. J. Gastroenterol.* ***93:*** 1614, (1998). 385 subjects with a history of food-induced heartburn participated in a single-dose, parallel, blinded, randomized, placebo-controlled trial. 60 minutes prior to receiving a standardized heartburn-inducing meal (chili and soft drink), subjects received either placebo, 10 mg famotidine (Pepcid AC), omeprazole 10 mg or omeprazole 20 mg. Subjects rated their heartburn symptom severity on a VAS scale beginning immediately prior to the meal, and at 30 min. intervals for 3 ½ hr postprandially. Compared to placebo, neither dose of omeprazole significantly prevented or reduced postprandial heartburn; 54, 52 and 55% of subjects treated with placebo, 10 mg omeprazole or 20 mg omeprazole reported moderate-to-severe post-prandial heartburn symptoms. In contrast, 34% of subjects treated with famotidine were heartburn free, and only 27% reported moderate to severe symptoms (consistent with previously published trials). 64% of subjects reported relief from 10 mg famotidine as good or excellent, compared to 40%, 42% and 47% treated with placebo, 10 mg omeprazole and 20 mg omeprazole, respectively ($p < 0.03$ vs. famotidine). Neither dose of omeprazole differed significantly from placebo for any efficacy parameter. This study showed a clear performance advantage for famotidine over omeprazole in prevention of meal-induced heartburn symptoms.

The present invention is directed to the recognition that a 10 or 20 mg dosage of omeprazole and a preferred acid neutralizing capacity of a bicarbonate salt is/will be sufficient to induce relief of heartburn symptoms without requiring additional dosing of the bicarbonate salt.

Study to prove effectiveness of a combination therapy in heartburn relief and prevention.

A suitable study involves administration of a provocative meal (chili, soft drink) to individuals who report suffering from meal-induced heartburn, and whose heartburn symptoms can be reproduced by the provocative meal and responds to antacid/acid neutralization treatment. Following development of heartburn, usually within 30 – 60 min of eating the meal, the combination of omeprazole and bicarbonate is administered in a randomized, blinded manner (10 – 20 mL containing 10 – 20 mEq (ANC) bicarbonate and 10 –20 mg omeprazole). Control treatments include bicarbonate alone, omeprazole alone, and placebo. Both the combination and bicarbonate treatments will provide rapid relief of heartburn symptoms, while lesser relief is attained with omeprazole and placebo (no difference between the latter treatments in degree of relief). A second heartburn provoking meal is then consumed at least 4 hours after the first meal, but no further treatments are administered. Those subjects who receive omeprazole-containing treatments after the initial meal experience a reduction in heartburn symptoms to the second meal. Subjects who receive antacid alone (bicarbonate) or placebo treatment with the first meal are expected to have fully recurrent symptoms to the later meal. Hence, the combination of bicarbonate + omeprazole provides for a rapid onset and a prolonged duration of heartburn relief.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples

herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

2. The method according to Claim 1 wherein the proton pump inhibitor is omeprazole, lansoprazole, pantoprazole, perprazole, or rabeprazole, or salts, isomers, enantiomers or derviatives thereof.

3. The method according to Claim 2 wherein the proton pump inhibitor is omeprazole.

4. The method according to Claim 3 wherein the dose of omeprazole is from about 10 to about 20mg.

5. The method according to any one of Claims 1 to 4 wherein the bicarbonate is sodium or potassium bicarbonate or a mixture thereof.

6. The method according to Claim 5 wherein the bicarbonate is sodium bicarbonate.

7. The method according to Claim 6 wherein the bicarbonate is administered in an ANC amount of about 18 to 40mEq.

8. The method according to Claim 1 wherein the proton pump inhibitor and alkali metal bicarbonate salt are administered in a solid unit dosage form.

8. The method according to Claim 8 wherein the dosage form is a compressed tablet.

9. The method according to Claim 8 wherein the dosage form is a capsule.

10. The method according to Claim 7 wherein the proton pump inhibitor is omeprazole and in a dosage range of from about 10 to about 20 mg.

11. The method according to Claim 1, wherein the pharmaceutical composition is a single unit dosage form administered in a volume of between approximately 10 ml and 20 ml of an aqueous solution.

12 The method according to Claim 11 wherein the dosage form is a sachet administered with water.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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US CL :424/717; 514/339
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,840,737 A (PHILLIPS) 24 November 1998, see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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(54) Title: AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION

(57) Abstract: The present invention relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salts, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solubilised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solubilising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION.

The present invention relates to an improved pharmaceutical composition and a process for its preparation. The present invention particularly relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salt, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solublised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solublising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

Benzimidazole derivatives such as Omeprazole, Lansoprazole Timoprazole and Pantoprazole etc., are known potent proton pump inhibitors with powerful inhibitory action against the secretion of gastric juice (Lancet, Nov. 27, 1982 pages 1223-1224). They are used in the treatment of Zollinzer – Elision syndrome and stress related esophagitis ulceration. The derivatives are well known and are described, for example in EP-A 0005129.

It has been found that these benzimidazole derivatives, and in particular omeprazole, are susceptible to degradation in acid and neutral media. It is known to protect oral dosage forms of such benzimidazole derivatives by providing an enteric coating. In this way, the active material is protected from acidic gastric juices until it reaches the desired site of release, e.g. the small intestine. Because certain enteric coatings themselves can be, or contain, acidic material, it also often is required to protect the benzimidazole derivatives from the acidity of the enteric coating. For example, it is known to formulate the benzimidazole derivatives with an alkaline material before applying the enteric coating. It is also known to provide an intermediate coating between the benzimidazole derivative and the enteric coating. Generally the intermediate coating is selected so as to be substantially water-soluble or water-dispersible.

EP-A-024 7983; US 4,786,505; US 4,853,230 and US 5,385,739 describe oral pharmaceutical preparations containing benzimidazole derivatives that are potent inhibitors of gastric acid secretion, which are composed of a core material in the form of small beads or tablets containing one of the

benzimidazole derivatives, particularly omeprazole, together with an alkaline reacting compound. The core material contains one or more inert reacting sub-coating layers thereon thereby providing a final outer enteric coating. Although the above-described compositions are reasonably stable over an extended period of storage, discoloration of the pellets and / or tablets with reduced gastric resistance and reduction of dissolution rate in alkaline buffers was observed.

Moreover the processes disclosed above are time-consuming and laborious, involving many stages in manufacturing of the composition, consequently increasing the cost of the final composition.

In a German patent DE 32 22 476 a pharmaceutical composition has been described in which a soft gelatin capsule that is resistant to digestive juice, whose wall includes a usual gelatin mass which contains polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate or a vinyl acetate / crotonic acid copolymer and/or an alkali metal salt, ammonia salt or amino salt of the same in their wall, and which released its contents readily in the intestines within the prescribed time. The capsules are further treated on the surface with an aldehyde-coating agent.

With the capsule shell composition described in DE 32 22 476 above, if used as such for manufacturing capsules containing one of the benzimidazole derivatives in a conventional manner, the free acidic groups of the polymer in the shell composition reacts with the benzimidazole derivatives and reduces the efficacy of the product during its storage / shelf life period.

The above said prior art processes also have the following drawbacks: -

Requirement of sophisticated coating equipment and large amounts of organic solvents / alkali salts are employed to dissolve the enteric polymers for coating the fine particles.

The active substance(s), benzimidazole derivatives, needs to be protected by a sub coat from the reacting acidic groups present in the enteric polymers.

The processing time and the number of steps involved are many.

The resulting product, i.e., pellets / beads / tablets, has to be dried to keep moisture content below 1.5% to ensure drug stability during processing and through its shelf storage.

The active substance(s), benzimidazole derivatives, present in the final formulation as solid dispersed in a hydrophilic solid matrix and hence requires some time to dissolve into the surrounding intestinal fluid before being absorbed.

Large quantities of polymer i.e. 15-25% w/w, based on product, need to be applied to achieve desired gastric protection.

The pH of medium used to suspend / solublise the drug needs to be adjusted to alkaline condition i.e. above pH 8.0 to prevent degradation during processing.

The micro environment surrounding the core also contains alkaline material to neutralise the acidic medium that permeates the outer enteric coating during the product transit through stomach.

In case of pellets / beads large surface area needs to be coated with protective polymer sub-coat.

Considering the importance gained for the composition containing benzimidazole derivatives, particularly for the treatment of duodenal ulcers, there is a need for the development of pharmaceutical composition containing said derivatives having stability for an extended period during which period the composition does not get discoloured and / or degraded.

The present invention is directed to the production of soft gelatin capsules in a conventional manner using gelatin mass having an enteric polymer incorporated into it and to incorporate a mixture containing benzimidazole derivative, and an alkaline reacting substance with larger quantities of hydrophobic oily substance or a mixture of such oily substances into the gelatin shell . The resulting capsules being insoluble up to a pH value of 5.5 in aqueous media, but quickly dissolving above a pH of 6.0.

The invention has been developed based on our finding as a result of sustained R & D work, that the incorporation of benzimidazole derivatives, particularly useful for the treatment of duodenal ulcers, along with an alkaline inert reacting material into a hydrophobic oily substance wherein the benzimidazole derivative is in the form of solution or dispersion, results in extended periods of stability during which period the composition does not get discolored and / or degraded.

In other words, the active ingredient in the composition is kept partially in the form of solution and partially in the form of finely divided particles suspended freely in the oily substance which makes the active ingredient readily absorbable the moment the gastric resistant but intestinal soluble gelatin composition is dissolved.

Such a composition will have an advantage over the existing form of the formulation as the available dosage forms for benzimidazole derivatives are having the total amount of active ingredient in the form of solid particles engulfed in a solid matrix of excipients preferably hydrophilic substances, further coated with protective and gastric resistant enteric polymer coatings. It may take some time to dissolve these coats before the benzimidazole derivative is dissolved into the surronding intestinal fluid and gets absorbed.

Accordingly the main objective of the present invention is to provide an improved pharmaceutical composition containing benzimidazole derivatives having enhanced stability during storage.

According to another objective of the present invention there is provided intestine dissoluble soft gel capsule composition comprising gelatin and an enteric polymer in the form of a free acid or its salt and the pharmaceutical composition comprises benzimidazole derivatives, in particular omeprazole, incorporated in an oily base which is stable during shelf storage.

Still another objective of the invention is to provide a pharmaceutical composition comprising benzimidazole derivatives, to be filled into soft gel capsules, which composition reduces degradation of the benzimidazole derivatives during storage / shelf life.

According to still another objective of the invention there is provided a process for preparation of soft gel capsules comprising benzimidazole derivatives that are resistant to the digestive / gastric juice, a gelatin mass and an enteric polymer in the form of a free acid or as its salt.

Accordingly, the present invention provides, an improved pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such

oily substances, an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent; the resulting capsules being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,

According to another feature of the present invention, there is provided a process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises forming a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, incorporating into the resultant capsule a composition comprising a benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, such substance(s) being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent.

The capsules so formed are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

In a preferred embodiment of the invention, the enteric polymer used in the soft gel capsule composition may be selected from among the polymers but not limited to free acid forms of hydroxypropyl methyl cellulose phthalate, alkylmethacrylate and methacrylic acid ester copolymers, polyvinylacetate phthalate and the like or their ammonia or alkali metal salts. The amount of such enteric polymer employed may range from 5.0 – 40.0 percent, preferably 5.0 – 25.0 percent by weight with reference to the dried shell.

The gelatin mass into which the enteric polymer is incorporated is made up of a composition known in the art and contains gelatin, a plasticizer, preservatives, colourants, opacifiers, flavours etc., as required.

In order to carry out faster dissolution of the enteric polymer for preparing the capsule shell composition, the polymer is first dispersed in water, then an aqueous solution of ammonia or alkali metal salt is mixed while stirring. When alkali metal salt is used it may be selected from substances such as sodium hydroxide, potassium hydroxide, bicarbonate sodium, potassium bicarbonate, sodium carbonate, potassium carbonate etc. The quantity of the base materials used is such that it is sufficient to neutralise 60 to 100 percent of the free acid groups present in the selected enteric polymer.

The excess ammonia or alkali has to be removed from the capsule shell composition to avoid decomposition of the ester couplings in enteric polymers. When aqueous ammonia solution is used to prepare polymer solution, the excess ammonia has to be removed before preparing the capsule after mixing with the gelatin mass, by mixing the mass under reduced pressure in warm condition.

When alkali metal salts are used, the excess alkali is to be neutralized by treating the capsules with an acid selected from any of the following ones, hydrochloric acid, sulphric acid, nitric acid, phosphoric acid, mono carboxylic acids such as acetic acid, propionic acid, benzoic acid etc., dicarboxylic acids such as oxalic acid, maleic acid, fumaric acid etc. The acids are used in the form of cold dilute aqueous solutions in the concentration range of 3 to 30% depending on the type of acid used. The acid treatment may be carried out after manufacturing and partial drying of the capsules to avoid deformation and / or leakage of the capsule contents.

According to another feature of the invention the soft gel capsules are optionally treated with a cross-linking agent that reacts with gelatin and makes it insoluble in gastric juice. The cross-linking agent may be selected from among the aldehydes such as formaldehyde, glutaraldehyde, crotonaldehyde 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde or carbodiimides like 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carbodiimide-metho-p-toluene-sulfonate. The treatment may be done by either coating 0.05 to 1.0% w/v of the substance in an alcohol containing aqueous solution on to the soft gel capsule surface or mixing these substances in the gelatin mass before capsule manufacturing.

According to another feature of the invention the pharmaceutical composition containing benzimidazole derivative, known for its potent proton pump inhibition with powerful inhibitory action against the secretion of gastric juice, is prepared by suspending and/or solubilising the benzimidazole derivative in a carrier mixture composed of a hydrophobic oily carrier material, an alkaline inert reacting material and a dispersing agent and/or a surface active agent. surface active agent. The amount of such benzimidazole derivative used is equivalent to one unit dose recommended depending on the benzimidazole derivative incorporated i.e. for omeprazole the amount incorporated into enteric soft gel capsule may range from 10.0 to 60.0mg per capsule, preferably 20.0 to 40.0 mg per capsule.

The hydrophobic oily material may be selected from among the following fats and oils: Fats and oils of vegetable origin such as sesame oil, corn, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil etc.; animal oils such as fish oil, pig oil, beef oil etc.; esters of straight chained aliphatic oils contained in glycerol such as Sunsoft 700 P-2 (a monoester substance manufactured by Taiho Chemicals Company) Panasete 810 (a triester substance, manufactured by Nippon Oils and Fats); hydrogenated vegetable oils or a mixture thereof. The amount of such hydrophobic oily material may range from 50.0 to 80.0 percent by weight with reference to the contents filled in a capsule.

The alkaline buffering material present in the pharmaceutical composition may be selected from among but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine etc. The amount of such alkaline buffering material present in the composition may range from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight with reference to the contents filled in capsule.

The substances that increase viscosity of the oily material either by dissolving or by forming a colloidal dispersion are used as dispersing agents. The dispersing agent is selected from among but not restricted to colloidal silicon dioxide, polyvinylpyrrolidone etc. The mount of such suspending agent present in the composition may range from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight with reference to the content filled in capsules.

The surface active agent used as solublising and / or dispersing agents is selected from among but is not restricted to substances such as glyceryl monostearate, polyoxyethylene castor oil derivatives such as Cremophor RH 40, Cremophor EL (Make : BASF Corporation), lecithin, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, doccusate sodium etc. The amount of such surface active agent present in the composition may range from 2.0 to 20.0 percent preferably 5.0 to 15.0 percent by weight with reference to contents filled in capsule.

The seamless soft gel capsules can be manufactured on a rotary die machine filling with the liquid and / or semi solid composition containing benzimidazole derivatives.

The invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE – 1

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methylcellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Lecithin	30.0

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule;

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 2

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament :

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 3

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	40.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	5.0
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 4

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	25.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	15.0

Gelatin mass containing hydroxypropyl methyl cellulose is prepared by dispersing hydroxypropyl methyl cellulose phthalate in the form of a fine powder in a mixture of glycerin and water maintained at 70°C in which gelatin is dispersed to dissolve forming the gelatin mass. After cooling the mass to 45°C, ammonia solution is added slowly along the stirrer rod while stirring into the gelatin preparation tank. Stirring is continued till hydroxypropyl methyl cellulose phthalate is completely dissolved. The mass is made bubble free by applying vacuum while maintaining the mass at 45 - 50°C under continuous mixing.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Cremohor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in soybean oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed in to the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 5

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Sodium hydroxide solution 1% w/v	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to sodium hydroxide solution at room temperature. Hydroxypropyl methyl cellulose phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Hydrogenated vegetable oil	85.0mg
Lecithin	20.0mg
Pantoprazole Sodium	45.0mg
Meglumine	20.0mg

Hydrogenated vegetable oil is melted and dispersed into soybean oil at 30 - 40°C followed by lecithin, meglumine and pantoprazole sodium and cooled to room temperature. The mixture is kneaded into a smooth paste using a triple roller mill.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 6

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Propylene glycol	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0

Gelatin mass is prepared by dispersing in water at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved in propylene glycol at 60 - 70°C. and mixed with the gelatin mass to obtain uniform mixture.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 7

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Polyvinylacetate phthalate (PVAP)	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinylacetate phthalate is dissolved by stirring into ammonia solution at room temperature. Polyvinylacetate phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Sunflower oil	200.0mg
Cremophor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in sunflower oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed into the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 8

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerine	10.0
Triethyl citrate	7.5
Water	20.0
Methacrylic acid co-polymer Type - C	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - C is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Colloidal silicon dioxide	6.0

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule;

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 9

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Polyvinyl acetate phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinyl acetate phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament :

Name of the ingredient	mg / Capsule
Sun flower oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into Sun flower oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 10

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	40.0
Triethyl citrate	7.5
Glycerin	10.0
Water	20.0
Methacrylic acid co-polymer Type - A	7.5
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water Triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - A is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Colloidal silicon dioxide	30.0mg

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

The advantages of the present invention are:

1) Simple method of manufacturing, when compared to the methods disclosed in the prior art making the process economical.

2) Improved bioavailability when compared to the solid enteric coated pellets and tablets as the medicament is solublised or suspended in the form of very fine particles in the liquid / semisolid pharmaceutical composition filled into the soft gel capsule.

3) The reactive acidic groups of enteric polymers are in minimal contact with the active ingredient as the polymer is mixed into large amount of gelatin mass. Only small amounts of alkaline reactive material is required to neutralize the free fatty acids in the oily substances and free acidic reacting groups of enteric polymer in contact with the active ingredient on inner surface of the shell.

4) The soft gel does not require any protective sub-coating. Consequently the active ingredient quickly dissolves into the intestinal fluid once the gastric resistant but intestinal soluble gelatin composition is dissolved.

5) The soft gel capsules are simple in composition and therefore do not require any sophisticated equipment for manufacturing.

We claim:

1. A pharmaceutical composition in form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises of a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer mixed into gelatin in the form of free acid or its salt and the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, an alkaline inert reacting material, a suspending agent, a surface active agent and / or a solublising agent; wherein the capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.

2. A pharmaceutical composition as claimed in claim 1 wherein the benzimidazole derivative, is selected from medicaments such as omeprazole, lansoprazole, pantoprazole, timoprazole and the like and the amount present in the formulation is equivalent to one unit dose of selected benzimidazole derivative.

3. A pharmaceutical composition as claimed in claims 1 & 2 wherein the enteric polymer employed for coating the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate and methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts and the amount employed ranging from 5.0 to 40.0 percent, preferably 5.0 to 25.0 percent by weight, with reference to the dried shell.

4. A pharmaceutical composition as claimed in claims 1 to 3 wherein the benzimidazole derivative in the formulation is suspended / solubilised in a hydrophobic oily substance selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof and the amount of hydrophobic oily substance used ranging from 50.0 to 80.0 percent by weight, with reference to the contents filled in capsules.

5. A pharmaceutical composition as claimed in claims 1 to 4 wherein substances such ascolloidal silicon dioxide, polyvinylpyrrolidone are used as dispersing agents in an amount ranging from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight and materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like are used as surface active agent and / or a solublising agent and the amount of surface active agent and/or solublising agent ranging from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

6. A pharmaceutical composition as claimed in claims 1 to 5 wherein materials such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like are used as alkaline inert reacting materials and the amount ranging from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight, with reference to the contents filled in capsule.

7. A pharmaceutical composition as claimed in claims 1 to 6 wherein the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide-metho-P-toluene-sulfonate and the like.

8. A pharmaceutical composition as claimed in claims 1 to 7 wherein the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

9. A process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments

which comprises forming a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer in the form of free acid or its salt, and incorporating into the resultant capsule a composition comprising of a benzimidazole derivative, a hydrophobic oily substance or a mixture of such substances, an alkaline inert reacting material, a suspending agent, a surface active agent and / or a solublising agent; where the resultant capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

10. A pharmaceutical composition in form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments substantially as herein described with reference to the examples.

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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

(57) Abstract: This invention provides a solid preparation without enteric coating which contains an acid labile active ingredient, particularly, a benzimidazole compound having an antiulcer action, and can neutralize the acid in stomach quickly, and exerts quickly the pharmacological effect of the active ingredient and suppresses the generation of a carbon dioxide gas as much as possible. A gastric disintegrable solid preparation contains an acid labile active ingredient, particularly, a benzimidazole compound, and at least one component selected from metal oxides and metal hydroxides. The preparation does not enteric-coated, but has a disintegration time of 7 minutes or less.

DESCRIPTION

STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

Technical Field

The present invention relates to a solid preparation, further in detail, to a medical solid preparation containing an acid labile active ingredient, particularly, an acid labile active ingredient such as a benzimidazole compound useful as an antiulcer agent.

Background Art

Benzimidazole compounds such as lansoprazole, omeprazole, rabeprazole and the like are widely used as a digestive ulcer therapeutic agent because of its gastric acid secretion suppressing action and gastric mucous membrane preventing action and the like.

However, these compounds have poor stability, and unstable to humidity, temperature and light. They are particularly unstable to an acid, and become extremely unstable in aqueous solution or suspension as the pH of the solution or suspension lowers.

In a preparation, namely, a tablet, powder, fine particles, capsule and the like, benzimidazole compounds become unstable since mutual interaction with other components of the preparation is stronger in a preparation

than that of the compounds alone, and consequently, coloration change or decomposition is observed in production and storage. For stabilization of them, JP-A 10-36290 discloses enteric granules or enteric fine particles obtained by compounding a stabilizer composed of an inorganic base salt of magnesium and/or calcium for a medical solid composition, then, applying an enteric coating.

However, for producing such an enteric preparation, a process is required in which fine particles or granules containing a benzimidazole compound are produced, then, an enteric coating is applied. Further, since it takes a longer time until an enteric film is dissolved and a medicine is absorbed in a digestive tract after administration, a quick pharmacological effect can not be expected in the early stages after administration.

On the other hand, USP 5,840,737 and WO 00/26185 disclose a solution, suspension, tablet and capsule obtained by combining omeprazole or lansoprazole, which is not enteric-coated, with an alkali metal salt of bicarbonate.

However, since these preparations are combined with a bicarbonate, they react with an acid in stomach to evolve carbon dioxide gas which causes burping, and therefore they are not preferable from the viewpoint of compliance.

Objects of the Invention

An object of the present invention is to provide a solid preparation having no enteric coating which is capable of neutralizing quickly an acid in stomach, realizing quick occurrence of pharmacological effect of an active ingredient, and suppressing the evolution of carbon dioxide gas as much as possible, by solving the above-mentioned problems in medical solid preparations containing an acid labile active ingredient typically including benzimidazole compounds.

Summary of the Invention

The present inventors have found that a metal oxide and/or metal hydroxide is suitable for a gastric acid neutralizing agent in a solid preparation containing an acid labile active ingredient and having no enteric coating, and further investigation resulted in completion of the present invention.

Namely, the present invention provides:

(1) A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides;

(2) A solid preparation according to the above-

mentioned (1), wherein the disintegration time is within 7 minutes;

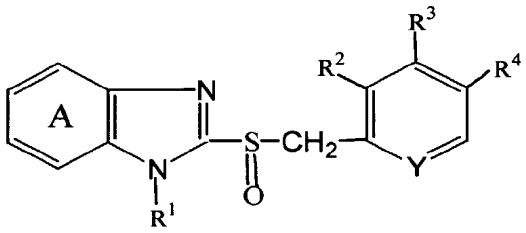
(3) A solid preparation according to the above-mentioned (1), which is the preparation without enteric coating;

(4) A solid preparation according to the above-mentioned (1), which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility;

(5) A solid preparation according to the above-mentioned (1), wherein an acid labile active ingredient is a proton pump inhibitor (hereinafter, referred to as "PPI");

(6) A solid preparation according to the above-mentioned (5), wherein the PPI is a benzimidazole compound;

(7) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring, R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the

same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof;

(8) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof;

(9) A solid preparation according to the above-mentioned (1), wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more;

(10) A solid preparation according to the above-mentioned (1) which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate;

(11) A solid preparation according to the above-mentioned (1) which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and coprecipitate of aluminum

hydroxide and sodium bicarbonate;

(12) A solid preparation according to the above-mentioned (4), wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate;

(13) A solid preparation according to the above-mentioned (4), wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine;

(14) A solid preparation according to the above-mentioned (1) which contains magnesium oxide;

(15) A solid preparation according to the above-mentioned (1) which contains magnesium hydroxide;

(16) A solid preparation according to the above-mentioned (1) which contains magnesium oxide and magnesium hydroxide;

(17) A solid preparation according to the above-mentioned (14) or (16), wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%;

(18) A solid preparation according to the above-mentioned (14), wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

(19) A solid preparation according to the above-mentioned (6), which contains at least one component

selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole compound;

(20) A solid preparation according to the above-mentioned (6), which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound;

(21) A solid preparation according to the above-mentioned (1), which is a tablet, a granule or a capsule;

(22) A solid preparation according to the above-mentioned (1), wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded; and

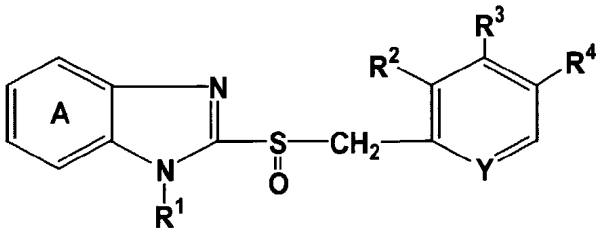
(23) A solid preparation according to the above-mentioned (4), wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are

separately compounded.

Detailed Description of the Invention

The acid labile active ingredient in the present invention is not particularly restricted, and any active components becoming unstable when exposed to gastric acid can be applied. Examples of the acid labile active ingredient include PPIs, erythromycin antibacterial compounds, anti-inflammatory enzymatic agents such as serrapeptase, semialkali proteinase and the like. Particularly, the present invention is suitable for PPIs. Such PPIs include benzimidazole compounds and similar compounds such as imidazopyridine compounds, e.g. tenatoprazole. Examples of benzimidazole compounds will be described below, however, the present invention is not limited to them and can be also applied to other active components unstable to an acid.

The benzimidazole compound which is a PPI, used in the present invention, includes a compound represented by the formula (I):



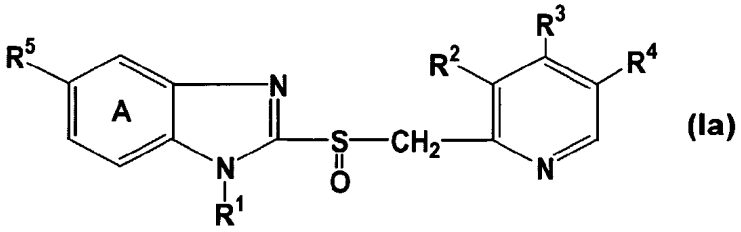
(I)

wherein, ring A represents an optionally substituted

benzene ring, R^1 represents a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

In the formula (I), the compound is preferably a compound wherein ring A is a benzene ring which may optionally have a substituent group selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy group and 5 or 6-membered heterocyclic group, R^1 is a hydrogen atom, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6} alkoxy group or optionally halogenated C_{1-6} alkoxy group, R^4 is a hydrogen atom or C_{1-6} alkyl group, and Y is a nitrogen atom.

Particularly preferable is the compound represented by the formula (Ia):



(Ia)

wherein, R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group or

C_{1-3} alkoxy group, R^3 is a C_{1-3} alkoxy group which may be halogenated or substituted by C_{1-3} alkoxy group, R^4 is a hydrogen atom or C_{1-3} alkyl group, and R^5 is a hydrogen atom, optionally halogenated C_{1-3} alkoxy group or pyrrolyl group (e.g., 1-, 2- or 3-pyrrolyl group).

In the formula (Ia), particularly preferable is the compound wherein R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group, R^3 is an optionally halogenated C_{1-3} alkoxy group, R^4 is a hydrogen atom, and R^5 is a hydrogen atom or an optionally halogenated C_{1-3} alkoxy group.

In the compound represented by the formula (I) above (hereinafter, referred to as compound (I)), the "substituent groups" in "an optionally substituted benzene ring" represented by ring A include, for example, a halogen atom, cyano group, nitro group, an optionally substituted alkyl groups, hydroxyl group, optionally substituted alkoxy group, aryl group, aryloxy group, carboxyl group, acyl group, acyloxy group, 5 to 10-membered heterocyclic group and the like, and 1 to 3 of these substituent groups may be substituted on a benzene ring. When the number of substituent groups is 2 or more, each substituent groups may be the same or different. Among these substituents, a halogen atom, an optionally substituted alkyl group and an optionally substituted alkoxy group are preferable.

As the halogen atom, a fluorine atom, chlorine atom,

bromine atom and the like are exemplified, among which a fluorine atom is preferable.

Examples of "alkyl group" in "an optionally substituted alkyl group" include C_{1-7} alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl and the like). Examples of "substituent group" in "an optionally substituted alkyl group" include a halogen atom, hydroxy group, C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy, etc.), C_{1-6} alkoxy-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), carbamoyl group and the like, and the number of these substituent groups may be 1 to 3. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

Examples of "alkoxy group" in "an optionally substituted alkoxy group" include C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, etc.). Examples of "substituent group" in "an optionally substituted alkoxy group" include groups identical with the "substituent group" of the "optionally substituted alkyl group" described above, and the number of substituent groups is also the same as that of the "optionally substituted alkyl group".

The "aryl group" includes, for example, C_{6-14} aryl

group (e.g., phenyl, 1-naphtyl, 2-naphthyl, biphenyl, 2-anthryl, etc.) and the like.

The "aryloxy group" includes, for example, C_{6-14} aryloxy group (e.g., phenyloxy, 1-naphtyloxy, 2-naphthyloxy, etc.) and the like.

The "acyl group" includes, for example, formyl, alkylcarbonyl, alkoxycarbony, carbamoyl, alkylcarbamoyl, alkylsulfinyl, alkylsulfonyl and the like.

The "alkylcarbonyl group" includes, for example, C_{1-6} alkyl-carbonyl group (e.g., acetyl, propionyl, etc.) and the like.

The "alkoxycarbonyl group" includes, for example, C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) and the like.

The "alkylcarbamoyl group" includes N-C_{1-6} alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), N,N-diC_{1-6} alkyl-carbamoyl group (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.) and the like.

The "alkylsulfinyl group" includes, for example, C_{1-7} alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, etc.) and the like.

The "alkylsulfonyl group" includes, for example, C_{1-7} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, etc.) and the like.

The "acyloxy group" includes, for example, alkylcarbonyloxy group, alkoxycarbonyloxy group, carbamoyloxy group, alkylcarbamoyloxy group, alkylsulfinyloxy group, alkylsulfonyloxy group and the like.

The "alkylcarbonyloxy group" includes C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, etc.) and the like.

The "alkoxycarbonyloxy group" includes, for example, C_{1-6} alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.) and the like.

The "alkylcarbamoyloxy group" includes C_{1-6} alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.) and the like.

The "alkylsulfinyloxy group" includes, for example, C_{1-7} alkyl-sulfinyloxy group (e.g., methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, isopropylsulfinyloxy, etc.) and the like.

The "alkylsulfonyloxy group" includes, for example, C_{1-7} alkyl-sulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy, etc.) and the like.

The "5 to 10-membered heterocyclic group" includes, for example, 5 to 10-membered (preferably, 5 or 6-membered) heterocyclic group having 1 or more (for example, 1 to 3)

hetero atoms selected from a nitrogen atom, sulfur atom and oxygen atom in addition to a carbon atom, and specific examples thereof include 2- or 3-thienyl group, 2-, 3- or 4-pyridyl group, 2- or 3-furyl group, 1-, 2- or 3-pyrrolyl group, 2-, 3-, 4-, 5- or 8-quinolyl group, 1-, 3-, 4- or 5-isoquinolyl group, 1-, 2- or 3-indolyl group and the like. Among them, preferable are 5 or 6-membered heterocyclic group such as 1-, 2- or 3-pyrrolyl group.

Preferably, ring A is a benzene ring which may have one or two substituent groups selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy groups and 5 or 6-membered heterocyclic group.

Examples of "aralkyl group" in "an optionally substituted aralkyl group" represented by R^1 include, for example, C_{7-16} aralkyl group (e.g., C_{6-10} aryl C_{1-6} alkyl group such as benzyl, phenetyl, etc.) and the like. Examples of "substituent group" in "an optionally substituted aralkyl group" include the same substituent groups as those of the "optionally substituted alkyl group" described above, and the number of substituent groups is 1 to 4. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

The "acyl group" represented by R^1 includes, for example, the "acyl group" exemplified as the substituent

group on ring A described above.

The "acyloxy group" represented by R^1 includes, for example, the "acyloxy group" exemplified as the substituent group on ring A described above.

Preferably, R^1 is a hydrogen atom.

The "optionally substituted alkyl group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkyl group" exemplified as the substituent group on ring A described above.

The "optionally substituted alkoxy group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkoxy group" exemplified as the substituent group on ring A described above.

The "optionally substituted amino group" represented by R^2, R^3 or R^4 includes, for example, amino group, mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, etc.), mono-C_{6-14} arylamino group (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di-C_{1-6} alkylamino group (e.g., dimethylamino, diethylamino, etc.), di-C_{6-14} arylamino group (e.g., diphenylamino, etc.) and the like.

Preferably, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group. More preferably, R^2 is a C_{1-3} alkyl group or C_{1-3} alkoxy group.

Preferably, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6}

alkoxy group or optionally halogenated C_{1-6} alkoxy group. More preferably, R^3 is a C_{1-3} alkoxy group which is halogenated or may be substituted with a C_{1-3} alkoxy group.

Preferably, R^4 is a hydrogen atom or C_{1-6} alkyl group. More preferably, R^4 is a hydrogen atom or C_{1-3} alkyl group (particularly, hydrogen atom).

Preferably, Y is a nitrogen atom.

Specific examples of the compound (I) include the following compounds.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, 2-[[3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole•sodium salt, 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and the like.

Among these compounds, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole(Lansoprazole) is preferable.

The above-mentioned compound (I) may be a racemic compound, or may be an optically active compound such as R-compound, S- compound and the like. For example, optically active substances such as (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (sometimes referred to as Lansoprazole R

enantiomer) may also be permissible and preferable.

The salt of the compound (I) is preferably a pharmaceutically acceptable salt, and examples thereof include salts with inorganic bases, salts with organic bases, salts with basic amino acids, and the like.

Suitable examples of the salt with an inorganic base include, for example, alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, etc.; ammonium salts, and the like.

Suitable examples of the salt with an organic base include, for example, salts with alkylamines (trimethylamine, triethylamine, etc.), heterocyclic amines (pyridine, picoline, etc.), alkanolamines (ethanolamine, diethanolamine, triethanolamine, etc.), dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

Suitable examples of the salt with a basic amino acid include, for example, salts with alginine, lysine, ornithine and the like.

Among these salts, alkali metal salts or alkaline earth metal salts are preferable. Particularly, sodium salts are preferable.

The compound (I) can be produced by a method known per se, and produced by methods described, for example, JP-A 61-50978, USP 4,628,098, JP-A 10-195068, WO 98/21201 and

the like, or methods according to these methods. The optically active compound (I) can be obtained by optical resolution methods (fractional re-crystallization method, chiral column method, diastereomer method, method using microorganism or enzyme, etc.), asymmetric oxidation and the like. For example, in the case of Lansoprazole R enantiomer, it can also be produced in accordance with the methods described in WO 00-78745, WO 01-83473, WO 01-87874 and WO 02-44167.

As the PPIs used in the present invention, the benzimidazole compound having an antiulcer action such as lansoprazole, omeprazole, rabeprazole and pantoprazole and the imidazopyridine compound such as tenatoprazole or optically active compounds thereof and pharmaceutically acceptable salts thereof are preferable.

The compounding amount of the benzimidazole compound used in the present invention varies depending on the kind and dosage of an active ingredient, and for example, the amount is from 0.001 to 0.3 parts by weight, preferably from 0.002 to 0.2 parts by weight relative to 1 part by weight of the solid preparation of the present invention.

The metal oxide and metal hydroxide used in the present invention are preferably those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more, and examples of the metal oxide include medical magnesium

oxide, magnesium silicate ($2MgO \cdot 3SiO_2 \cdot xH_2O$), dry aluminum hydroxide gel ($Al_2O_3 \cdot xH_2O$), magnesium metasilicate aluminate ($Al_2O_3 \cdot MgO \cdot 2SiO_2 \cdot xH_2O$) and the like. Particularly, magnesium oxide can be suitably used.

Preferable magnesium oxides are those that are available for medical use and that have an excellent reactivity to acid and neutralization ability. As these magnesium oxides, magnesium oxide obtained by a usual production method and commercially available magnesium oxide can be used, and preferable is one obtained by calcination at low temperature, so-called, calcining magnesia. The magnesium oxide calcined at a temperature of about 500 to about 1000°C is generally preferable, and particularly from the viewpoint of neutralization ability the magnesium oxide calcined at a temperature of about 600 to about 900°C is preferable, and the magnesium oxide calcined at about 800°C is most preferable. Among these magnesium oxides, favorable is the one that neutralizes the environment prior to the release of the acid labile active ingredient by the disintegration of the preparation in stomach and has the function to enhance the remaining ratio of the active ingredient. Such magnesium oxide is preferably the one that has usually a BET specific surface area of about $10m^2/g$ to about $50m^2/g$, preferably about $20m^2/g$ to about $50m^2/g$.

Hereupon, a BET specific surface area means the specific surface area measured by nitrogen gas adsorption method, and the specific surface area containing the surface of given amount magnesium oxide and its cavity in which nitrogen gas can enter is determined by the amount of adsorbed nitrogen gas.

The magnesium oxide includes, for example, commercially available heavy magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), heavy magnesium oxide (Tomita Pharmaceutical Co. Ltd.), heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), light magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) and the like. Particularly heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) is preferable.

The metal hydroxide includes, for example, medical magnesium hydroxide, aluminum hydroxide, synthetic hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$), co-precipitate of aluminum hydroxide and magnesium hydroxide, co-precipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and co-precipitate of aluminum hydroxide and sodium hydrogen carbonate. Among these compounds, magnesium hydroxide is particularly preferable from the viewpoint of the disintegrating property and dissolution property of a preparation.

These may be used alone or in combination of two or

more. Some of metal oxides and metal hydroxides may whittle the surface of a preparation apparatus in production. As a result of such whittling, the resulting tablets sometimes become partially or wholly darkish or blackish and are imparted with black spots, lines or surfaces. Sticking of the resulting preparations on a die in production of tablets is also sometimes caused, depending on the metal hydroxides or metal oxides used. These properties deteriorate remarkably the productivity. It has been found that, when metal oxides or metal hydroxides having whittling property and adhesiveness on a die are used, the whittling action and adhesiveness on a die can be suppressed by wet or dry granulation using metal oxides or metal hydroxides having no such properties or pharmaceutically acceptable additives described bellow (excipients, binders, disintegrants, etc.) in combination. In the case of preparations of PPIs, preferred are magnesium hydroxides, magnesium oxides and combination of a magnesium hydroxide and magnesium oxide from the viewpoint of compatibility with PPIs, dissolution property, and disintegrating property of a preparation.

These metal oxides and/or metal hydroxides are compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach,

preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. Metal oxides and metal hydroxides are compounded usually in an amount of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1000 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of an acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each metal oxide and metal hydroxide. For example, metal oxides and metal hydroxides are compounded in an amount of about 0.1 to 1500 parts by weight, preferably about 0.5 to 800 parts by weight, more preferably 0.1 to 400 parts by weight relative to 1 part by weight of a benzimidazole compound. When the active ingredient is a benzimidazole compound, the pH in stomach usually increases simultaneously with initiation of dosing, and they are compounded preferably in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

Usually, metal oxides and metal hydroxides are compounded preferably in an amount that pH increases to 7 or more within 10 minutes, more preferably within 7 minutes, by a measuring method as shown in the following experiment example.

In the present invention, at least one component selected from carbonates of alkaline earth metals and basic additives having high water-solubility may be compounded, in addition to these metal oxides and/or metal hydroxides, if necessary. The carbonates of alkaline earth metals include, for example, calcium carbonate and magnesium carbonate for medical use. The basic additives having high water-solubility include medical additives having an antacid action such as trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate, L-arginine and the like. These may also be used alone or in combination of two or more.

These are also compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid, and are compounded usually in a total amount with metal oxides and metal hydroxides of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1200 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of a acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each additives.

Usually, neutralization agents are compounded in a total amount of 0.1 to 1800 parts by weight, preferably about 0.5 to 1000 parts by weight, more preferably 1 to 800 parts by weight relative to 1 part by weight of a benzimidazole compound. Preferably, they are compounded in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

In the solid preparation of the present invention, additives can be further used such as excipients for preparation (e.g., glucose, fructose, lactose, sucrose, D-mannitol, erythritol, maltitol, trehalose, sorbitol, corn starch, potato starch, wheat starch, rice starch, microcrystalline cellulose (crystalline cellulose), anhydrous silic acid, anhydrous calcium phosphate, precipitated calcium carbonate, calcium silicate, etc.), binder (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, etc.), disintegrating agent (e.g., low-substituted hydroxypropylcellulose, calmellose, calmellose calcium, carboxymethyl starch sodium, cross calmellose sodium, crospovidone, hydroxypropyl starch, etc.), flavoring agent (e.g., citric acid, ascorbic acid,

tartaric acid, malic acid, aspartame, acesulfam potassium, somatin, saccharin sodium, dipotasium glycirrhizinate, sodium glutamate, sodium 5'-inosinate, sodium 5'-guanylate, etc), surfactant (e.g., polysorbate, polyoxyethylene•polyoxypropylene copolymer, sodium laurylsulfate, etc.), aromatics (e.g., lemon oil, orange oil, menthol, peppermint oil, etc.), lubricant (e.g., magnesium stearate, sucrose fatty acid ester, stearyl sodium fumarate, stearic acid, talc, polyethylene glycol, etc.), coloring agent (e.g., edible yellow No. 5, edible blue No. 2, ferric oxide, yellow ferric oxide, etc.) and antioxidant (e.g., sodium ascorbate, L-cysteine, sodium sulfite, etc.).

The particle size of a raw material used in them is not particularly restricted, and preferably 500 μm or less from the standpoint of a production property and dosing property.

The method of producing the solid preparation of the present invention may be a method known per se, and for example, benzimidazole compounds, metal oxides and/or metal hydroxides, if necessary, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and an antacid action, excipients, further, binders, disintegrating agents, lubricants, flavoring agents, coloring agents, aromatics are combined suitably to

give a tablet, powder, granule, capsule, fine particles and the like. These can be produced by a method described in the preparation general rule of The Pharmacopoeia of Japan, 14th revision.

Particularly, the granulation by wet granulation is preferred.

Herein, the wet granulation means a method for obtaining granulated materials or powders such as granules and fine granules by granulating a dispersion or solution of the mixture of a drug and excipient in water, binder or solvent and then drying, and the granulation mechanism may be any type such as extrusion, fluidization, rolling, centrifuging, stirring, spraying etc.

Further, these preparations may be coated with a coating agent (for example, coating film containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, etc.), however, an enteric coating is not applied.

In the present invention, preparation raw materials may be formulated in one portion, or may be divided into two or more groups and formulated (for example, layer separation, granulations having different disintegrating properties, etc.). In any case, metal oxides and/or metal hydroxides, further, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and

an antacid property are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, and prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. For example, a method in which a group containing an active ingredient is compounded near the nucleus of a preparation and a metal oxide and/or metal hydroxide is compounded in an outer layer of the preparation are exemplified.

Also in either case of one-group formulation or divided or separate-groups formulation, it is possible to neutralize gastric acid by compounding a basic additive having high water solubility and dissolving it quickly.

Further, by dividing preparation raw materials into a group containing an acid labile active ingredient and a group containing no active ingredient and compounding them separately in the preparation to give a time difference of disintegration of components, the group containing no active component can be formulated to disintegrate more quickly. A metal oxide and/or metal hydroxide may be compounded in both groups or in the group containing no active ingredient. Further, a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action may be compounded in

either group or both groups.

Furthermore, a preparation containing a group which contains neither an active ingredient nor a metal oxide and metal hydroxide but contains mainly a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action, may also be formulated. Particularly, this preparation is suitable to increase the pH in stomach by dissolving this group more quickly.

Further, when the components are grouped and formulated separately, an additive having bonding ability to a group containing an active ingredient (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, polyethylene oxide, carboxymethylethylcellulose, carboxyvinyl polymer, ethylcellulose, ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer, etc.) may be compounded to delay the dissolution of the active ingredient. Further, a group containing an active component may be coated to delay the dissolution with a component containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol,

polyvinylpyrrolidone, ethylcellulose or ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer.

More specifically, a tablet can be produced, for example, by several methods such that a benzimidazole compound, metal hydroxide, excipient, binder, disintegrating agent and lubricant are mixed and compressed directly into tablets; a benzimidazole compound, a metal hydroxide, excipient and additive having high water solubility and an antacid action are mixed, then, a binder is added to the mixture to form granules, and a disintegrating agent and lubricant are added to the granules, and then the resultant mixture is compressed into tablets; and a benzimidazole compound, a metal hydroxide and excipient are mixed, then, a binder is added to the mixture to obtain granules, and separately, a metal hydroxide, additive having high water solubility and an antacid action and excipent are mixed, then, a binder is added to the mixture to obtain granules, and these obtained granules, disintegrating agent and lubricant are mixed and compressed into tablets.

Further, in the case of production of two or more kinds of granules, it is also possible that one or more kinds of binders are added to a group containing a benzimidazole compound to suppress its dissolution.

Granules can be produced by an ordinary method. For example, granules can be produced by the same methods as the production methods of a tablet, or by an extrusion granulation method. For obtaining granules having higher sphericity and smaller particle size distribution, for example, nucleus-containing granules may be produced by a method described in JP-A 63-301816. Nucleus-containing granules are obtained by coating a powdery spray agent containing a benzimidazole compound having an antiulcer action, metal hydroxide, excipient, disintegrating agent and the like while spraying binding liquid such as hydroxypropylcellulose on a sugar nucleus. The nucleus granule includes, for example, Nonparell obtained by coating sucrose (75 parts by weight) with corn starch (25 parts by weight) by a method known per se, and spherical nucleus granules using crystalline cellulose, and further, the nucleus granule itself may be the active ingredient component mentioned above. The average particle size of the nucleus granule is generally 14 to 80 mesh.

In the case of a capsule, it can be obtained by filling with a simply mixed powder or the particles for a tablet or granule obtained above.

The solid preparation obtained in the present invention is a gastric disintegrable solid preparation without enteric coating having an disintegration time of 7

minutes or less, preferably 5 minutes or less, more preferably 4 minutes or less, by the measurement of disintegrating time based on the method described in United States Pharmacopoeia <701> Disintegration.

The solid preparation of the present invention can be itself administered orally. The solid preparation of the present invention can be taken in the form of liquid or semisolid by dispersing or dissolving it previously in water, juice, yoghurt and the like.

In the solid preparation of the present invention, when the active ingredient is, for example, a benzimidazole compound represented by the formula (I) such as lansoprazole and optically active compounds thereof, these compounds are useful as a medicine since they have excellent antiulcer action, gastric acid secretion-suppressing action, mucous membrane protecting action, anti-Helicobacter pylori action and the like, and have low toxicity. In this case, the solid preparation of the present invention can be orally administered to mammal animals (for example, human, monkey, sheep, horse, dog, cat, rabbit, rat, mouse, etc.), for the purpose of treating and preventing peptic ulcer (for example, gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, Gastroesophageal Reflux Diseases (GERD) e.g. reflux esophagitis, Symptomatic GERD, erosive

esophagitis; NUD (Non Ulcer Dyspepsia), stomach cancer (including stomach cancer caused by promotion of production of interleukin-1ß by gene polymorphism of interleukin-1), stomach MALT lymphoma and the like, removing Helicobacter pylori, suppression of upper digestive canal hemorrhage caused by peptic ulcer, acute stress ulcer, and hemorrhagic gastritis, suppressing upper digestive canal hemorrhage caused by invasive stress (stress caused by cerebral vascular disorder requiring major operation or intensive care needing intensive management after operation, head trauma, multi-organ disorder, wider range heat injury), treating and preventing ulcer ascribed to nonsteroidal anti-inflammatory agent; and treating and preventing gastric hyperacidity and ulcer by stress after operation. For removal of Helicobacter pylori, it is preferable to use the solid preparation and, penicillin antibiotics (e.g., amoxicillin) and erythromycin antibiotics (e.g., clarithromycin), together.

The preparation of this invention is especially applicable for GERD (e.g., Symptomatic GERD and erosive esophagitis).

The daily dose differs depending on severity of symptom, age, sex and body weight of the patient, period and interval of administration, kind of the active ingredient employed and the like, and is not particularly

restricted, and for example, the solid preparation can be administered as an antiulcer agent to an adult (60 kg) at an oral daily dose of about 0.5 to 1500 mg/day, preferably about 5 to 150 mg/day as an active ingredient. These benzimidazole compound-containing preparations may be administered once or in two or three divided portions a day.

Examples

Hereinafter, the present invention is further detailed by the following Examples, which are not intended to restrict the present invention.

Example 1

Production of active ingredient group

240 g of lansoprazole, 1160 g of magnesium hydroxide, 616 g of D-mannitol and 264 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 120 g of hydroxypropylcellulose in 1380 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2188 g of granules.

Production of outer layer group

870 g of magnesium hydroxide, 1107 g of D-mannitol and 474 g of corn starch were charged in a fluidized bed granulator, and 750 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2199 g

of granules.

300 g of a active ingredient group, 408.5 g of an outer layer group, 37.5 g of crospovidone and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 2

Production of active ingredient group

120 g of lansoprazole, 200 g of magnesium hydroxide, 580 g of D-mannitol and 240 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1161.1 g of granules.

Production of outer layer group

720 g of magnesium hydroxide, 259.5 g of D-mannitol, 225 g of microcrystalline cellulose (Ceolus KG-801) and 112.5 g of crospovidone were charged in a fluidized bed granulator, and 500 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1138.8 g of granules.

300 g of a active ingredient group, 439 g of an outer layer group and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 3

Production of active ingredient group

120 g of lansoprazole, 580 g of magnesium hydroxide, 332 g of D-mannitol and 108 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 982.1 g of granules.

Production of outer layer group

108.8 g of magnesium hydroxide, 453.8 g of trometamol, 52.5 g of D-mannitol, 127.5 g of microcrystalline cellulose (Ceolus KG-801) and 63.7 g of crospovidone were charged in a fluidized bed granulator, and 400 g of purified water was sprayed, and these materials were granulated, and dried to obtain 758.7 g of granules.

270 g of a active ingredient group, 483.8 g of an outer layer group and 11.2 g of magnesium stearate were

mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (850 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 4

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., grade: heavy N), 725 g of magnesium hydroxide, 1390 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and 2.8% aqueous solution prepared by dissolving 70 g of hydroxypropylcellulose in 2430 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.5 g of granules.

2614.5 g of the obtained granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 5

60 g of lansoprazole, 120 g of magnesium oxide, 406 g of magnesium hydroxide and 584 g of D-mannitol were charged into a fluidized bed granulator, and 5.6% aqueous solution prepared by dissolving 28 g of hydroxypropylcellulose in 472 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1144.3 g of granules.

581 g of the granules, 70 g of microcrystalline cellulose (Ceolus KG-801), 35 g of crospovidone and 14 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 6

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1316.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2817.7 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 7

105 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1300.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2754.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled

powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 8

75 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1391.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2828.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 9

52.5 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g

of magnesium hydroxide, 1352.8 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 10

300 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1166.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.5 g of yellow ferric oxide and 1 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried

to obtain 2783.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 11

210 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1195.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.45 g of yellow ferric oxide and 1.05 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2823.7 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel

edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 12

150 g of lansoprazole, 700 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 435 g of magnesium hydroxide, 1406.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 1906.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2756.4 g of granules.

2614.5 g of the granules, 350 g of microcrystalline cellulose (Ceolus KG-801), 175 g of crospovidone and 70 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using a tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Experiment Example 1

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 1.

Table 1

	Example 1	Example 2	Example 3
Average disintegration time (min)	0.92	0.70	0.45

Measurement of pH change

Test solution of 0.05 mol hydrochloric acid 100 mL (37 ℃) was charged into a 100 mL beaker, and each one tablet obtained in example 1, example 2 and example 3 was added and a test was carried out under the condition of 100 revolutions per minute using a basket according to the dissolution test method of USP. pH change by time was measured.

As shown in Table 2, pH of the test solution increased quickly, and pH of 7 or more could be reached over 3 minutes.

Table 2

	1 min	2 min	3 min	4 min	5 min	10 min
Example 1	1.42	3.12	7.63	8.83	9.04	9.15
Example 2	2.01	6.77	7.97	8.46	8.64	8.85
Example 3	3.08	6.99	7.49	7.72	7.83	8.06

Measurement of dissolution profile

One tablet obtained in example 1, example 2 or example 3, or one Takepron capsule (30 mg) filled with lansoprazole granules with an enteric coating was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured under rotation at 75 rpm by the absorbancy at 286 nm in the ultraviolet range, and the dissolution ratio was calculated.

The results are shown in Table 3.

The dissolution profile was quick as compared with the dissolution of a capsule.

Table 3

	5 min	10 min	15 min	20 min
Example 1	91.8%	97.9%	98.2%	97.5%
Example 2	99.4%	101.9%	101.1%	100.3%
Example 3	81.5%	87.7%	88.3%	87.7%
Capsule	38.1%	94.2%	96.8%	97.7%

Experiment Example 2

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 4.

Table 4

	Example 4	Example 5
disintegration time (min)	1.25	1.28

Measurement of dissolution profile

One tablet obtained in example 4 or example 5 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with that of the above-mentioned Takepron capsule.

The results are shown in Table 5.

Table 5

	5 min	10 min	15 min	20 min
Example 4	86.4%	95.8%	97.5%	97.5%
Example 5	93.3%	96.9%	96.2%	95.7%

Experiment Example 3

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 6.

Table 6

	Example 6	Example 7	Example 8	Example 9
disintegration time (min)	1.8	1.98	1.95	1.98

Measurement of dissolution profile

One tablet obtained in example 6, example 7, example 8

or example 9 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with the dissolution of the capsule described above.

The results are shown in Table 7.

Table 7

	5 min	10 min	15 min	20 min
Example 6	78.7%	88.3%	90.0%	90.7%
Example 7	54.9%	81.1%	86.6%	87.6%
Example 8	76.4%	91.8%	96.2%	97.2%
Example 9	78.1%	92.5%	97.6%	96.2%

Experiment Example 4

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 8.

Table 8

	Example 10	Example 11	Example 12
disintegration time (min)	1.60	1.28	1.52

Measurement of dissolution profile

One tablet obtained in example 10, example 11 or example 12 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The results are shown in Table 9.

The dissolution profile was quick as compared with that of a capsule mentioned above.

Table 9

	5 min	10 min	15 min	20 min
Example 10	73.7%	82.4%	83.7%	83.7%
Example 11	59.1%	72.6%	76.4%	78.8%
Example 12	85.4%	95.2%	96.7%	97.9%

Industrial Applicability

The medical solid preparation of the present invention can be obtained by a simple production method since no enteric coating is applied, though containing an acid labile active ingredient, for example, a benzimidazole compound which is a PPI. Further, since the initial dissolution of an active component from the preparation is quicker as compared with a preparation with an enteric coating, the initiation time of a pharmacological action can be shortened. Furthermore, since a metal oxide and

metal hydroxide is mainly used for neutralization and stabilization in stomach, the generation of carbon dioxide gas which is generated in stomach by the administration of a preparation containing a bicarbonate or carbonate in a large amount can be suppressed, and therefore burp can be suppressed in the preparation.

CLAIMS

1. A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides.

2. A solid preparation according to claim 1, wherein the disintegration time is within 7 minutes.

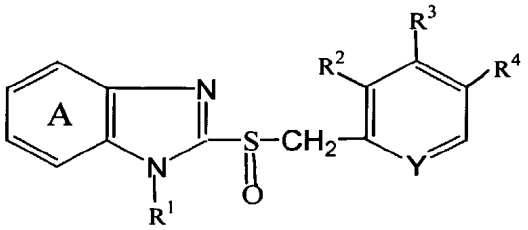
3. A solid preparation according to claim 1, which is the preparation without enteric coating.

4. A solid preparation according to claim 1, which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility.

5. A solid preparation according to claim 1, wherein an acid labile active ingredient is a proton pump inhibitor (PPI).

6. A solid preparation according to claim 5, wherein the PPI is a benzimidazole compound.

7. A solid preparation according to claim 6, wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring,

R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

8. A solid preparation according to claim 6, wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof.

9. A solid preparation according to claim 1, wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1 % aqueous suspension has a pH of 8.0 or more.

10. A solid preparation according to claim 1 which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate.

11. A solid preparation according to claim 1 which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and

coprecipitate of aluminum hydroxide and sodium bicarbonate.

12. A solid preparation according to claim 4, wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate.

13. A solid preparation according to claim 4, wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine.

14. A solid preparation according to claim 1 which contains magnesium oxide.

15. A solid preparation according to claim 1 which contains magnesium hydroxide.

16. A solid preparation according to claim 1 which contains magnesium oxide and magnesium hydroxide.

17. A solid preparation according to claim 14 or claim 16, wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%.

18. A solid preparation according to claim 14, wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

19. A solid preparation according to claim 6, which contains at least one component selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole

compound.

20. A solid preparation according to claim 6, which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound.

21. A solid preparation according to claim 1, which is a tablet, a granule or a capsule.

22. A solid preparation according to claim 1, wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded.

23. A solid preparation according to claim 4, wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are separately compounded.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 51050 A (UNIV MISSOURI) 19 July 2001 (2001-07-19) page 31, line 13,14 See examples I-C, I-D, I-E. ---	1-23
X Y	EP 1 004 305 A (EISAI CO LTD) 31 May 2000 (2000-05-31) examples 24-26; table 3 ---	1-9, 19-23 1-23
X	WO 01 28559 A (EISAI) 26 April 2001 (2001-04-26) examples 4,5; table 2 See table 2, examples 4,5: disintegration time claims 1,2 --- -/--	1-3,5-9, 19-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2002	16/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 235 311 B1 (ULLAH ISMAT ET AL) 22 May 2001 (2001-05-22) Example 1: Tablet comprising: Pravastatin, Magnesium Oxide, Magnesium Carbonate. column 1, line 31,32	1-4,9-23
X	WO 97 25066 A (ASTRA AB ;DEPUI HELENE (SE); HALLGREN AGNETA (SE)) 17 July 1997 (1997-07-17) page 23, line 21-30	1-4,9-23
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 15, 6 April 2001 (2001-04-06) & JP 2000 355540 A (EISAI CO LTD), 26 December 2000 (2000-12-26) abstract	1,3,5-9
X	TETSURO TABATA ET AL: "STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 18, no. 13, 1992, pages 1437-1447, XP002921226 ISSN: 0363-9045	1,3, 5-10,14, 21
Y	See table 5, magnesium oxide.	1-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims 22 and 23 relate to compositions according to claims 1 comprising " a group containing an acid labile ingredient and a group containing a metal oxide or metal hydroxide but containing no active ingredient". No reference to any "group" is made in claim 1. Claims 22 and 23 are therefore considered not clear. Consequently the search has been carried out for the compositions as claimed in claims 1-21 and the ones described in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/08704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/08704

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